EVALUATING THE ROLE OF URINARY PSA IN DIFFERENTIATING BENIGN PROSTATE HYPERPLASIA FROM CARCINOMA PROSTATE

A THESIS SUBMITTED TO

BABA FARID UNIVERSITY OF HEALTH SCIENCES, FARIDKOT (PUNJAB)

IN THE PARTIAL FULFILLMENT

FOR THE AWARD OF DEGREE OF

M.Ch.

IN

UROLOGY

MAY 2022

Submitted By

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DECLARATION BY THE CANDIDATE

I hereby declare that the thesis entitled "**EVALUATING THE ROLE OF URINARY PSA IN DIFFERENTIATING BENIGN PROSTATE HYPERPLASIA FROM CARCINOMA PROSTATE**" submitted towards partial fulfillment of the requirements for the award of **M.Ch in Urology** degree to BFUHS is a compilation of original work carried out by me under the supervision of Dr Arvind Goyal, Associate Professor, Dr. Sandeep Sharma, Professor & Head, Department of Urology and Dr. Navjot Bajwa, Professor & Head, Department of Biochemistry. No part of this thesis has formed the basis for the award of any degree previously.

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Dedicated
to
My Family
&
Teachers

ACKNOWLEDGEMENT

Learning is not attained by chance; it requires blessings of a teacher to learn and grow

First of all, I humbly bow down to and thank God Almighty for enlightening the path and being the guiding force through all ups and downs in this journey. I hereby take opportunity to thank all the inspiring souls and experts whose presence and contribution has been crucial during the process.

I find myself short of words while expressing my profound sense of gratitude and sincere thanks towards my respected teacher, guide and supervisor, ***Dr. Arvind Goyal****, Associate Professor, Department of Urology, Dayanand Medical College and Hospital, Ludhiana for his untiring efforts, careful and reasoned criticism and painstaking supervision. His immense knowledge of the subject and analytical gaze has always been a great source of inspiration for me. I thank him for his patience and timely advice, without which I would have floundered in my study. His ardent interest, precious suggestions and constant encouragement at each step have contributed the most in materialization of this thesis work.*

Words cannot express my gratitude to my honourable teacher and co-guide, ***Dr. Sandeep Sharma****, Professor and Head of Department of Urology, Dayanand Medical College and Hospital, Ludhiana. His boundless expression of knowledge, guidance and constant supervision has gone a long way in ensuring the completion of this study. He has always provided the best encouragement and facilities that helped me to overcome whatever obstacles came during the course and brought this manuscript to see the light of the day.*

With immense regards, I would like to express my gratitude towards my revered co-guide, ***Dr. Navjot Bajwa****, Professor & Head of Department of Biochemistry, Dayanand Medical College and Hospital, Ludhiana for his never-ending support, invaluable academic*

guidance and rational opinions which scaffolded necessary steps for the construction of this study.

With due decorum, I extend a token of sincere thanks to ***Dr. Harmandeep Singh Chahal****, Associate Professor and* ***Dr. Ravi Angral*** *Senior Consultant, Department of Urology, Dayanand Medical College and Hospital, Ludhiana for their invaluable advice and guidance throughout the course of this study.*

"Above all I am greatly indebted to my family members for their innumerable sacrifices, my mother ***Mrs. Neelam Gorka,*** *my wife* ***Dr. Swati Tidyal*** *& my little daughter* ***Rinaya,*** *who are responsible for what I am today and who have stood by me through good and hard times like pillars. I am eternally indebted to them for always believing in me and providing with their valuable love and support throughout my life.*

I take this opportunity to thank my lovely seniors ***Dr. Vipul & Dr. Tariq,*** *who have always inspired me through their hard work and motivation. I thank my colleague –cum friend* ***Dr. Azhar Anwar*** *for sharing the highs and lows of residency life. Also, I would like to extend my gratitude to the technical and non –technical staff of my department for their timely support required for the completion of this thesis.*

I duly acknowledge Mrs. Niharika, Mr. Naveen and all the R&D staff for their skilful analysis and typing of the manuscript carefully.

Lastly but certainly not the least, I acknowledge the help of all those invisible hands who are responsible for the successful outcome of this dissertation.

Dr. Vivek Gorka

LIST OF ABBREVIATIONS

AAT	Anti-Androgen Therapy
BPH	Benign Prostate Hyperplasia
DNA	Deoxyribonucleic Acid
DRE	Digital Rectal Examination
FDA	Food And Drug Administration
fPSA	Free PSA
GST-P1	Glutathione-S-Transferase-P1
IPD	In-Patients Department
KLK3	Kallikrein Related Peptidase 3
MiRNA	Micro RNA
MRI	Magnetic Resonance Imaging
MSMB	Microseminoprotein-Beta
MS-PCR	Methylation Specific Polymerase Chain Reaction
OPD	Out-Patients Department
PAP	Prostatic Acid Phosphatase
Pca	Prostate Carcinoma
PCA3	Prostate Cancer Antigen-3
PSA	Prostate Specific Antigen
PSAD	Prostate Specific Antigen Density
PSMA PET Scan	Prostate Specific Membrane Antigen Positron Emission Tomography Scan
RNA	Ribonucleic Acid
RP	Radical Prostatectomy
RRP	Retropubic Radical Prostatectomy
S100A8/A9	Inflammatory Markers and Member Of The S100 Family Of Proteins.
tPSA	Total PSA
TRUS	Transrectal Ultrasonography
UTI	Urinary Tract Infection
S.PSA	Serum PSA
U.PSA	Urinary PSA

ABSTRACT

Introduction: Serum PSA is a known marker for carcinoma prostate. But when serum PSA is in equivocal range (4-10 ng/dl), it may be associated with or without findings on DRE, Urinary PSA has its role to play in differentiating carcinoma prostate from BPH.

Aim of Study: 1. To determine the association of urinary PSA in differentiating benign prostate hyperplasia and carcinoma prostate.

2. To study its role in diagnosis carcinoma prostate in cases when serum PSA is in equivocal range.

Materials & Methods: After clearance from institutional ethical committee and informed written consent from all those patients who fulfill the criteria was taken up for the study. A urine sample before DRE and immediately after DRE was collected for urinary PSA level. TRUS guided prostate biopsy was taken from all the patients and sent for histopathological examination.

Results: Total of 31 patients were included in our study, of which 24 patients were diagnosed as benign prostate hyperplasia and 7 patients were diagnosed as carcinoma prostate. The median serum PSA was 6.34 and 9.55 ng/dl in BPH and carcinoma prostate respectively. The change in urinary PSA from pre-DRE to post DRE and PSAD in BPH was significantly different (p value < 0.05) when compared to prostate carcinoma.

Conclusion: Carcinoma prostate has significant morbidity and mortality as well. When serum PSA is in equivocal range, urinary PSA has significant role in diagnosing carcinoma prostate and differentiating it from other benign disorders of prostate like BPH.

Keywords: serum prostate specific antigen, urinary pre and post DRE PSA prostate carcinoma, digital rectal examination, transrectal ultrasonography.

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INTRODUCTION

PSA is a glycoprotein enzyme encoded in humans by KLK3 gene that is produced exclusively by the epithelial cells of all types of prostatic tissue, benign as well as malignant. Physiologically, it is present in the seminal fluid at high concentration and functions to break the high molecular weight protein responsible for the seminal coagulum into smaller polypeptides. This action results in liquefaction of the coagulum. Its expression is also confirmed in extra prostatic tissues of male or female origin such as: breast, thyroid, pancreas, uterus, placenta and salivary glands.

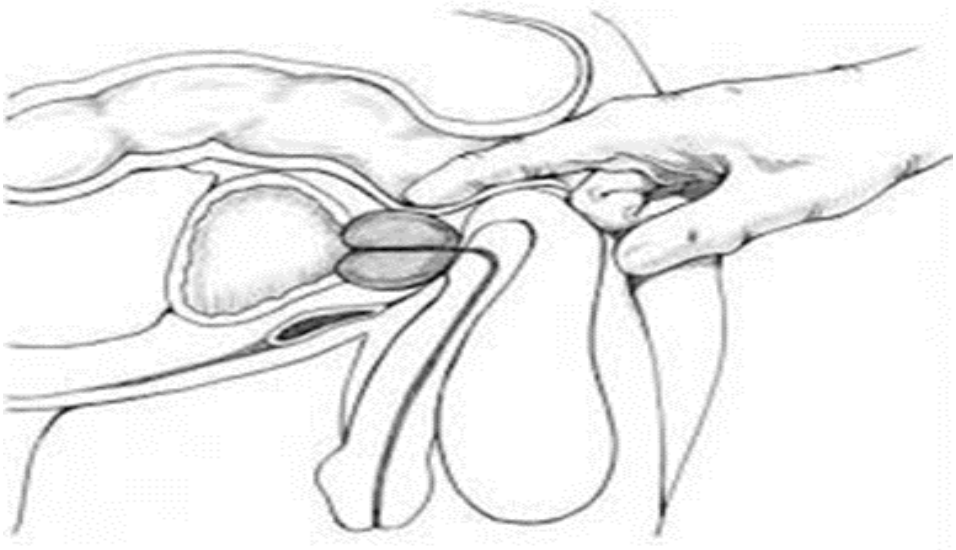
PSA is also present in the serum and can be measured reliably by either a monoclonal immunoradiometric assay or a polyclonal radioimmunoassay. The calculated half-life of serum PSA ranges from 2.2 to 3.2 days and the metabolic clearance rate of this tumour marker follows first-order kinetics. Digital rectal examination, cystoscopic examination and prostate biopsy all can cause false elevation of the serum PSA concentration. Conditions such as bacterial prostatitis and acute urinary retention can also spuriously elevate the serum PSA level and approximately 25% of the patients with BPH have an elevated serum PSA concentration as well.[1]

PSA was reported and published in the Journal of Reproduction and Fertility and in the Journal of Immunology as early as in 1970 in USA. Biochemically, PSA in seminal fluid in its free form has a molecular weight of about 30,000 daltons while in serum, where it occurs in the complex form with alpha1-chymotrypsin, its molecular weight is approximately 100,000 daltons being comparable to that of prostatic acid phosphatase.[2]

Serum prostatic specific antigen (PSA) has been proven to be a generally reliable indicator in the diagnosis and management of prostate cancer. Abnormal findings on digital rectal examination

associated with increased serum prostate specific antigen level are evaluated by prostatic biopsy. However, not all patients with increased PSA requires prostate biopsy because it may be raised in variety of benign prostate conditions as mentioned above. Serum PSA has revolutionized the management and follow-up of the patients with prostate cancer. There are many non-invasive modalities including biomarkers in serum, urine and semen such as DNA, RNA and glycoproteins for diagnosing carcinoma prostate.[3,4]

Digital rectal examination results in the drainage of prostatic secretions. Thus, urinary sample after digital rectal examination of prostate results in expulsion of secretions into urethra and hence, large quantity of prostatic secretions will be present in the urine. These prostatic secretions have various types of chemical substances such as different forms of PSA, glycoproteins, miRNA etc. which may differ in their quantity in various pathological conditions of prostate. However, the concentration of PSA in urine never becomes zero even after removing whole of prostate gland because of persistence of periurethral glands and minor prostatic glands which continuously secretes PSA in urine. Although the concentration of PSA is very low in urine.[5]



Picture 1: Palpation of Prostate during Digital Rectal examination

In the recent years, urine has become one of the most interesting and useful biofluid due to presence of different kind of markers in different prostatic conditions (benign as well as malignant). Urine contains about more than 2000 proteins including membrane, extracellular and lysosomal proteins. Urine can be stored for several months under -20^{o}C and for several years under -80^{o}C thus, making it further, a very attractive biofluid.[6]

PSA consists of a polypeptide and one N-linked oligosaccharide chain. However, it comprises of heterogenous molecules differing in the polypeptide backbone as well as in the carbohydrate composition resulting in the existence of different molecular forms as PSA isoforms. It has been seen that the expression and degeneration of different PSA isoforms can be specifically related to different pathophysiological states of the prostate.

Free PSA (fPSA) rather than total PSA (tPSA) and its ratio of free-to-total PSA in serum may improve the diagnostic specificity by 15–20%. Free PSA escapes its cleavage by binding to chymotrypsin and thus, its level is increased in carcinoma prostate. This type of test is recommended for patients who present with serum PSA levels within the “grey-zone” of 4.0 to 10.0 ng/ml. Earlier, it was thought that high level of free PSA was associated with benign prostate tissue as compared to prostate carcinoma. However, this test too had inconsistencies in later studies due to which it is not widely implemented as a screening tool. The precursor of PSA i.e. pro PSA, has emerged as a promising biomarker due to its ability to differentiate between prostate carcinoma and BPH, where its level appears to be raised in prostate carcinoma. In one large prospective study of patients with prostate carcinoma, it is shown that the percentage of pro PSA has the specificity to 44.9% and sensitivity of 80% for detecting prostate carcinoma in comparison to total and free PSA which is having specificity of 30.8% and 34.6% respectively.[7,8]

Also, it has been observed that PSA glycoforms in carcinoma prostate is different from PSA glycoforms in benign prostate hyperplasia. Screening of different glycoforms is done by liquid chromatography-tandem mass spectrometry with ion accumulation. Normally, abundance of each glycoform is different in both carcinoma prostate and benign prostate hyperplasia.[9]

The variation in various molecular forms of PSA is not well defined in comparison to structural properties of PSA which helps in distinguishing between benign (BPH) and malignant (prostate carcinoma) disorders of prostate despite calculating PSA alone. PSA from benign prostate tissue has molecular mass in the range of 6-28 kDa whereas PSA from cancer tissue doesn't contain low molecular mass forms.

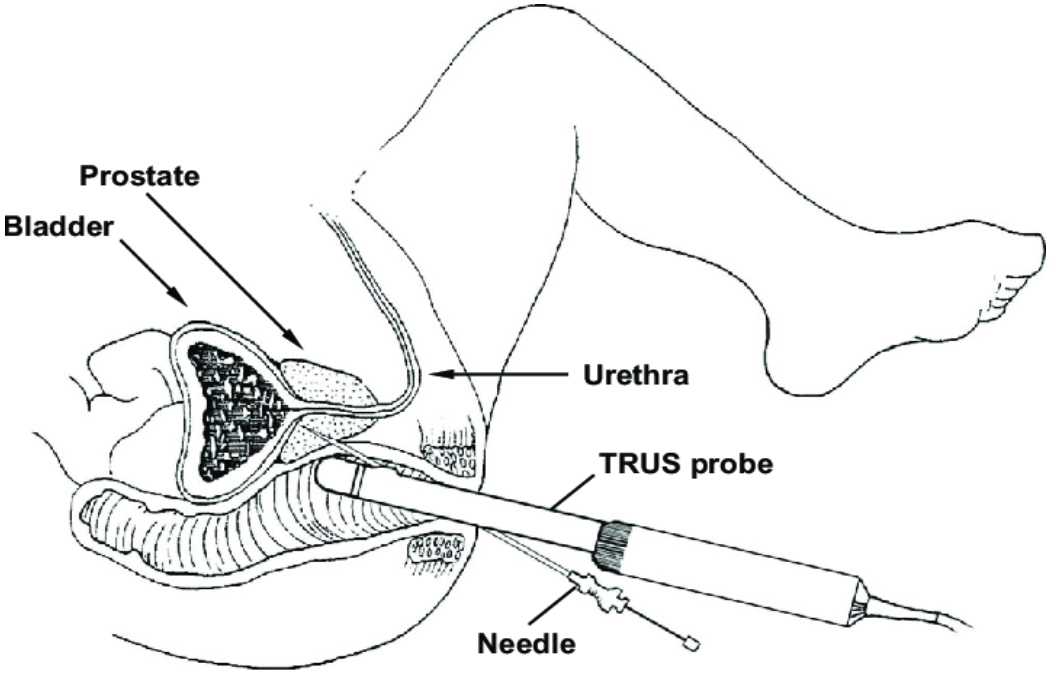
Most of carcinoma prostate arises from peripheral zone of prostate except for 20-30% which originates from transitional zone. Benign prostate hyperplasia arises mostly from transitional zone. As symptoms of both prostatic carcinoma and BPH are same; therefore, it is very difficult to differentiate depending upon the symptomatology.[10]

PSA is organ specific but it is not cancer specific since it could be raised in some other conditions of prostate e.g., prostatitis, UTI, etc. PSA density is calculated as total PSA (ng/ml) divided by total volume of prostate in ml. PSA density might help the clinician in biopsy decision with the cut off value of 0.10 ng/ml^2. PSA density helps in the detection of aggressive carcinoma prostate and also reduces number of unnecessary prostate biopsies. Similarly, PSA velocity i.e. measure of the rate of increase in serum PSA over time, helps significantly and increases the chance of detection of prostate carcinoma from benign prostate hyperplasia.[11]

PCA3 is a non coding RNA which is excessively produced by prostate cancer cells. Due to its unstable nature, a more reliable and efficient RNA extraction method to extract it from serum, urine and prostate tissue is needed. However, there are certain methods like magnetic

bead with poly-T functionalization and capturer strand as compared to traditional methods like the phenol-chloroform method and the affinity column method which results in efficient RNA extraction. As PCA3 is expressed in large quantity in prostate cancer cells, its yield in urine samples can aid in screening, detection and diagnosing prostate carcinoma without the need for more invasive tests like prostate biopsy.[12]

Transrectal ultrasonography is considered as the gold standard for prostate imaging and guided biopsy for histological diagnosis. It too has certain limitations such as painful procedure, haematuria, hematospermia, urinary retention, UTI and sepsis. As per guidelines, a prophylactic dose of broad-spectrum antibiotic should be given to the patient at the time of TRUS guided prostate biopsy. An extended 12 core biopsy usually associated with more pain as compared to sextant biopsy but it is sufficient for reporting histopathological specimen.[13]



Picture 2: Trans Rectal Ultrasonography

Multiparametric MRI is a non-invasive tool and continues to show increased accuracy for the detection, localization, risk stratification and staging of prostate carcinoma for patients. But it again has limitations such as high cost, limited availability, errors in interpretations.[14]

There is still very little literature known about the possible role of urinary PSA in the diagnosis or follow-up of prostate cancer. All cancers diagnosed on biopsy are not aggressive and need treatment. Thus, a biopsy showing clinically insignificant cancer may not require treatment and a biopsy may miss a significant cancer that would require treatment otherwise. Therefore, the aim of our study is to evaluate the usefulness of urinary PSA in differentiating between benign prostatic hyperplasia (BPH) and prostate cancer, especially when serum PSA is in equivocal range.

AIMS AND OBJECTIVES

1. To determine the association of urinary PSA in differentiating benign prostate hyperplasia and carcinoma prostate.

2. To study its role in diagnosing carcinoma prostate in cases when serum PSA is in equivocal range.

REVIEW OF LITERATURE

Prostate cancer is the second most common cause of cancer death in males. Serum PSA remains the best single test for the detection of early prostate cancer and multiple variations have been studied to improve its sensitivity and specificity, first by associating it with the digital rectal examination and then by looking at age-adjusted PSA, PSA density, PSA velocity and percent free PSA. The upper limit of normal PSA (4.0 ng/ml) can also be lowered to 2.5 ng/ml or even lower because 20%–30% of tumours will be missed if the only method of detection is serum PSA with a cut off of 4.0 ng/ml.[15]

PSA is the most widely used screening test for prostate cancer and any increase in PSA is considered to be the main cause of the stage migration recently observed. The ratio of free to total PSA (%fPSA) has been shown to increase PSA accuracy in cancer detection; however, few screening studies have systematically evaluated its role in cancer detection rates in men with PSA levels <4.0 ng/ml and normal DRE.[7]

Although prostate carcinoma screening is widely utilized nowadays, two thirds of the biopsies performed are still unnecessary because patient may not be the candidate for aggressive treatment for prostate carcinoma due to multiple comorbidities, low grade tumour histology (GS <6) on biopsy, life expectancy less than 10 years or initiating the hormonal treatment may increase the morbidity of the patient. Thus, the discovery of non-invasive prostate carcinoma biomarkers remains necessary. In recent years, the utilization of urine has emerged as an attractive option for the non-invasive detection of prostate carcinoma.[16]

Prostate-specific antigen (PSA) is the single most important tumour marker in early detection and monitoring of prostate cancer. However, routine analysis of serum PSA concentrations does not allow differentiation between prostate carcinoma and benign prostatic diseases. Determination of the serum-to-urinary PSA ratio enhances the specificity of PSA in screening of prostate carcinoma and follow up

of patients with prostate carcinoma under androgen deprivation therapy.[17,18]

Benign prostatic hyperplasia (BPH) is associated with significantly higher urinary levels of prostate-specific antigen (PSA) than in prostate cancer. The clinical value of the Serum PSA to Urine PSA ratio helps the patients for diagnosis of prostate carcinoma, particularly when the pre-biopsy serum level of PSA lies between 4.0 and 10.0 ng/ml.[18] Expressed prostatic secretions represents the fluid being secreted by the prostate following a digital rectal prostate massage, which in turn can be collected in post-examination voided urine.[19]

Of all PSA-based markers, only the FDA-approved prostate health index (PHI) which includes PSA, fPSA and pro PSA, shows improved specificity over isolated percentage of free PSA(%fPSA) and total PSA. Other serum kallikreins or sarcosine in serum or urine show more variable data.[7] In urine, the FDA-approved prostate cancer gene 3 (PCA3) has also proven its utility in the detection and management of early prostate carcinoma when compared with PSA and %fPSA.[12]

The role of most urinary proteomics in the diagnosis of prostate cancer is undefined. Levels of urinary biomarkers such as prostate-specific antigen and microseminoprotein-beta (MSMB) may differ between men with and without prostate carcinoma. Urinary samples taken before and after prostatic massage shows significant differences in the concentration of urinary PSA and MSMB in both benign prostate hyperplasia and carcinoma prostate patients. Prashant Shrivastava et al. in their study concluded that patients who were diagnosed as benign prostate hyperplasia showed significant increase in post DRE urinary PSA level when compared to post DRE urinary PSA of prostate carcinoma patients.[20]

The cancer detection rate with 16-core TRUS-guided biopsy is significantly higher than that with 10-core biopsy (54.76% vs. 15.09%, $p<0.001$). In patients with both normal and abnormal DRE findings, 16-

core biopsy has a better detection rate than the 10-core biopsy protocol.[13]

In some cases, however, urine PSA levels can be elevated in men with local tumour recurrence after Radical Prostatectomy (RP) when serum levels are still undetectably low. This indicates that the determination of urinary PSA concentration might be useful in the follow-up of patients after RP.[21,22]

Tremblay et al. studied the mode of excretion of three prostatic secretory proteins; namely acid phosphatase (PAP), prostate-specific antigen (PSA) and beta-inhibin, in the urine of normal adult men. As there was high variability in the level of these proteins during day time, 24 hours urine samples were collected. The study showed that PAP concentrations in 50% of men with or without symptomatic BPH were similar to those of control group. In the remaining 50%, PAP was undetectable. In contrast, average PSA and beta-inhibin concentrations were higher in patients with BPH than in control group (normal young men with no carcinoma prostate) with p value less than 0.05. The three markers were decreased or non-detectable in about half of the patients with untreated prostatic cancer and this phenomenon was observed more in patients who were treated for prostate carcinoma.[23]

Ravery et al. concluded that cancer secretes more serum PSA per volume of prostate gland than benign prostatic hyperplasia. PSA density (PSAD, serum PSA divided by the volume of the entire prostate) has been suggested as an additional diagnostic criterion. They studied 153 men with prostatomegaly and PSA values between 4 and 10 ng/ml (by Hybritech assay), the volume of the prostate was determined by transrectal ultrasonography and 6 systematic biopsies were performed. The groups with positive and negative biopsies respectively were compared according to age of the patient, results of DRE and PSAD. Histological grade of positive biopsies and pathological stage of patients who underwent radical prostatectomy were also compared with diagnostic criteria. Prostate cancer was found

in 45 of 153 men (29.4%). Patient's age had no influence on detection rates. The positive predictive value of a PSAD ≥ 0.2 was twice the positive predictive value of a PSAD below 0.2, irrespective of DRE findings. Thus, an increasing number of positive biopsies were associated with increasing PSAD and histological grade.[11]

Robert G Uzzo et al. studied role of percent free PSA in men with a total PSA between 2 and 10 ng/ml. Men with a normal DRE and total PSA between 2 and 4 ng/mL were advised to undergo transrectal ultrasound-guided (TRUS) biopsies of the prostate if the percent free PSA was less than 27%. The primary endpoint evaluated was prostate cancer detection in high-risk men with a benign prostate examination on DRE, a normal total PSA between 2 and 4 ng/ml and percent free PSA less than 27%. They concluded that a percent free PSA of less than 27% was found to be useful for detecting early-stage but clinically significant cancers in men with a total PSA value between 2 and 4 ng/mL and normal DRE findings.[8]

Prashant Shrivastava et al. studied the role of urinary PSA and urinary microseminoprotein beta in Seventy-seven patients. They were divided into two groups: 32 had PCa (Group A) and 45 had no cancer (Group B) on biopsy. The median (interquartile range) serum PSA was 49.6 (0.2–254) ng/ml. The median urine PSA (29.5 vs. 26.4 mg/dl) and MSMB (1.7 vs. 2.4 mg/dl) were similar in both groups at baseline. However, post-DRE, both these metabolites increased significantly in Group B but not in Group A, resulting in significantly higher post-to-pre values in Group B versus Group A. The post-DRE urine PSA/MSMB ratio was also significantly different between the groups.[20]

Chun-Jen Hsiao et al identified some PSA glycoforms such as Hex5HexNAc4NeuAc1dHex1, and monosialylated, sialylated, and unfucosylated glycoforms that differed significantly between the prostate cancer and benign prostate hyperplasia samples. Also, these glycoform have detection sensitivity of 87.5% and specificity of 60% for prostate cancer identification which is higher than those of the serum

PSA marker; Thus, reducing unnecessary invasive procedures and financial burden on patient for diagnosing carcinoma prostate.[9]

Miroslava M Jankovic et al. examined the structural (glycosylation) characteristics of urinary PSA. They separated urinary PSA of patients diagnosed with benign prostate hyperplasia and carcinoma prostate by ion-exchange chromatography and subsequently characterized by means of lectin affinity chromatography using plant lectins with different carbohydrate specificities as ligands. The main differences observed were in the lectin reactivity to Four isoforms (Ulex europaeus agglutinin, Aleuria aurantia agglutinin, Phaseolus vulgaris erythroagglutinin and Phaseolus vulgaris leucoagglutinin) of urinary PSA from both BPH and PCa samples that were separated by ion-exchange chromatography.[24]

Kristina Stuopelyte et al. evaluated the importance miRNA in prostatic tissue, serum and urine. In their study, they successfully detected several miRNA from urine samples of patients suffering from prostate carcinoma and BPH. MiRNA-375 increased expression in urine whereas miRNA-148a decreased expression in urine and increased expression in prostatic tissue significantly improved the specificity and sensitivity of PSA in patients who falls in equivocal range of PSA(4-10 ng/ml).[25]

Seok Joong Yun et al. compared mRNA, protein, and urinary Nucleic acid levels of S100A8 and S100A9 between prostate cancer and BPH patients. Both S100A8 and S100A9 are inflammatory markers for infections and inflammatory conditions. S100A8 and S100A9 levels are lower in prostate carcinoma than BPH. But in more aggressive prostate carcinoma and carcinoma prostate with shorter biochemical free recurrence time, the expression of these markers is increased. Urinary cell-free nucleic acid levels of S100A8/A9 follows same kinetics of expression levels as obtained from tissue staining; thus, these markers in urine and tissue have both diagnostic and prognostic importance in prostate carcinoma.[26]

Radu Minciu et al. determined the importance of hypermethylation of glutathione-s-transferase P1 (GST-P1) in differentiating prostate carcinoma from benign prostate hyperplasia. In their study, 31 patients were included in a group of histopathological proven prostate carcinoma and 34 patients were included in BPH group. The genomic DNA was extracted from the urine of patients and was analysed for methylation by MS-PCR (methylation specific polymerase chain reaction). Out of 31, 27 patients had hypermethylation in prostate carcinoma group while 4 patients in BPH group had hypermethylation in whom second biopsy was done, that confirmed the diagnosis of prostate adenocarcinoma in these patients. From this study, they concluded that hypermethylation of GST-P1 emerged as a new molecular biomarker in urine which can help in early diagnosis of prostate carcinoma and in differentiating between prostate carcinoma and benign prostatic lesions.[27]

Pejcic T et al. conducted a study between January 2001 and November 2003 on 142 patients who were divided into seven groups;

1. Young and healthy volunteers,
2. BPH-24 group: patients with benign prostatic hyperplasia (BPH) in whom 24-hour urine was collected for estimation of urinary PSA
3. BPH-I group: patients with BPH who collected the first portion of the voided urine.
4. TRUS-prostate carcinoma group: patients with prostate carcinoma which gave the first portion of urine just prior to transrectal ultrasound- guided prostate biopsy (TRUS- biopsy),
5. TRUS-non-prostate carcinoma group: patients who gave first portion of urine prior to TRUS-biopsy, but biopsy did not prove the presence of prostate carcinoma,
6. RRP group: patients, who underwent radical retropubic prostatectomy (RRP),
7. AAT group: patients who underwent anti-androgen or androgen deprivation therapy.

They concluded that urinary PSA does not help in differentiating patients with prostate carcinoma from benign prostate hyperplasia rather it has positive correlation with size, aggressiveness of tumour and local stage of disease in which the concentration of urinary PSA is decreased in urine because of large size of tumour and local spread. Urinary PSA helps in early detection of hormone resistance and thus prompt change of therapy as required. It also helps in follow up of patients who are on androgen deprivation therapy or post operative case of radical prostatectomy. [28]

MATERIALS AND METHODS

After clearance from institutional ethical committee and informed written consent, all the patients who fulfil the criteria were taken up for the study.

SOURCE OF DATA

This prospective study was conducted in department of Urology & Kidney Transplant in IPD and OPD patients at Dayanand Medical College & Hospital from March 2020 to February 2021.

METHOD OF COLLECTION OF DATA

Inclusion Criteria

- Patients of age group between 50 years and 80 years presenting with lower urinary tract symptoms.
- Increased S.PSA level (4-10ng/dl)
- 24 hours of last ejaculation

Exclusion criteria

- Active urinary tract infection,
- Patients with features of prostatitis,
- Diagnosed case of carcinoma prostate,
- Prostatic abscess.

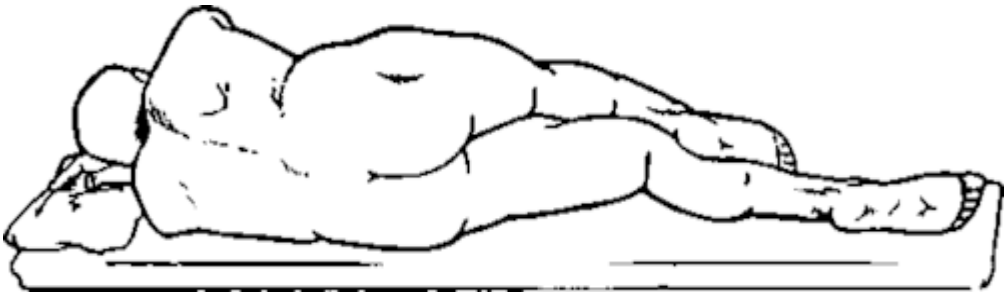
Demographic profile of all the patients was noted down.

Methodology

After explaining about the procedure and taking informed consent for study as well as prostate biopsy (TRUS guided), all those patients who have S.PSA> 4 up to 10 ng/ml (normal serum PSA value = 0 to 4 ng/ml) were taken up for our study.

A urine sample before DRE and immediately after DRE was collected for urinary PSA level. During DRE, whole of the prostate gland was pressed sufficiently from all the sides. The urinary samples were collected in sterile containers and sent to biochemistry laboratory

DMCH immediately for analysis by the standard biochemical analysers. Both Pre DRE and post DRE urinary samples were labelled separately.



Picture 3: Position (Sims) for Digital Rectal Examination

The urinary as well as serum PSA was assessed by Access Hybritect PSA assay, which is a paramagnetic particle, electro-chemiluminescent (ECLIA) immunoassay for the quantitative determination of total prostate specific antigen(PSA) levels.

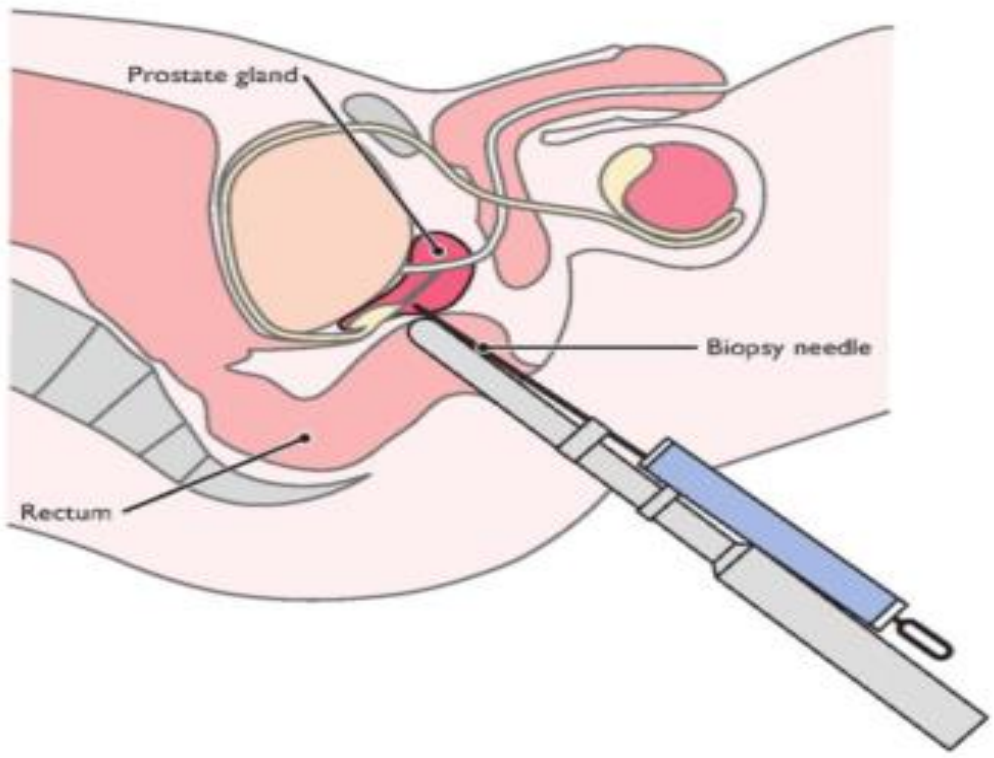
Now as per study protocol patients were explained, counselled and advised for TRUS guided prostate biopsy. Informed consent was taken before every TRUS guided biopsy after expanding the risks and complications. Patients were laid down in left lateral position (Sims position).

Ultrasound machine used for TRUS guided prostate biopsy is a product of Fujifilm (Sonosite edge II). The ultrasound probe used for TRUS was TVS probe. Under all aseptic precautions, a condom was applied over the TVS probe and a needle guide, which is attached to the ultrasound probe for prostate gun. The TVS probe was lubricated with lignocaine jelly 2% and inserted into rectum. Prostate gland was localized and thoroughly evaluated for any abnormality if present.

Sextant biopsies protocol was followed for any hypoechoic lesion/area within the prostate gland and if no abnormality was detected during transrectal ultrasonography, then 12 core biopsies were taken from both the lobes (base to apex) in different containers.

The prostate biopsies containers were labelled separately for each core corresponding to the prostate area/location from where they were

taken. The containers were filled with formaldehyde solution 10 % as a preservative solution and were sent to Department of Pathology, DMCH for final histopathology and immunohistochemistry of the specimen



Picture 4: TRUS Guided Prostate Biopsy

Depending upon the final histopathology report, patients who were diagnosed with carcinoma prostate were labelled as group A and those who were diagnosed as BPH were labelled as group B. After completing the study protocol, each patient was advised for further treatment plan for their better wellbeing.

OUTCOME: There are no standard guidelines regarding the evaluation of patients with serum PSA in the range of 4-10 ng/ml associated with normal digital rectal examination. In this study, we tried to establish the role of urinary PSA in the diagnosis of carcinoma prostate there by

limiting the need for prostate biopsy and other radiological investigations such as MP MRI/ PSMA PET CT scan in every case.

STATISTICAL ANALYSIS

The continuous data was expressed as mean ± SD and the categorical data expressed as proportions. The difference between the groups for continuous data was analyzed by t-test or Mann-Whitney U test based on the normality of the data. Normality was assessed by Shapiro-Wilk test. The difference in the categorical data between the two groups was analyzed by Fisher's exact test. $P < 0.05$ was considered significant. The data was analyzed using SPSS version 26 program.

Ethical Issues

After approval of the study from the Institutional Ethics Committee, informed written consent was taken from all participants. All the patients were explained that their identity would remain confidential and the sensitive data would be used for research purposes only. The study followed the principles of Helsinki.

OBSERVATIONS AND RESULTS

This prospective study was conducted in Department of Urology & Kidney Transplant, in both IPD and OPD patients, at Dayanand Medical College & Hospital from March 2020 to February 2021. After clearance from institutional ethical committee and informed written consent, all those patients who fulfilled the criteria were taken up for the study.

1. Baseline Characteristics

Baseline characteristics were evaluated in our study population in which mean age was 67.7 ± 7.2 years and 68.2 ± 8.8 years for BPH group (24 subjects) and the Carcinoma Prostate group (7 subjects) respectively, which is comparable across both the groups. The other parameters at baseline which we assessed were serum PSA, prostate size, pre-DRE-Urinary PSA, post-DRE-Urinary PSA and PSAD.

The Baseline demographic data were compared between the two groups as mentioned in the table below

Table 1: Baseline characteristics

	BPH (n=24)			**Ca Prostate (n=7)**			**P value[$]**
Age(yrs.)	67.7± 7.2			68.2 ± 8.8			
	Median	IQR		Median	IQR		
Sr.PSA[#]	6.34	5.03	8	9.55	9	10	0.016
Prostate size[#]	36	30	46.4	67	43.5	86.5	0.012
Pre-DRE-Ur. PSA[#]	67.5	30.30	196.12	246.9	66.8	569	0.023
Post-DRE-Ur. PSA#	1048.8	494.2	2259.8	860	315.5	2512	0.041
PSAD[#]	0.104	0.082	0.131	0.235	0.215	0.3	0.033

Data in Mean ± SD; # Data in Median (IQR); $ Mann-Whitney U

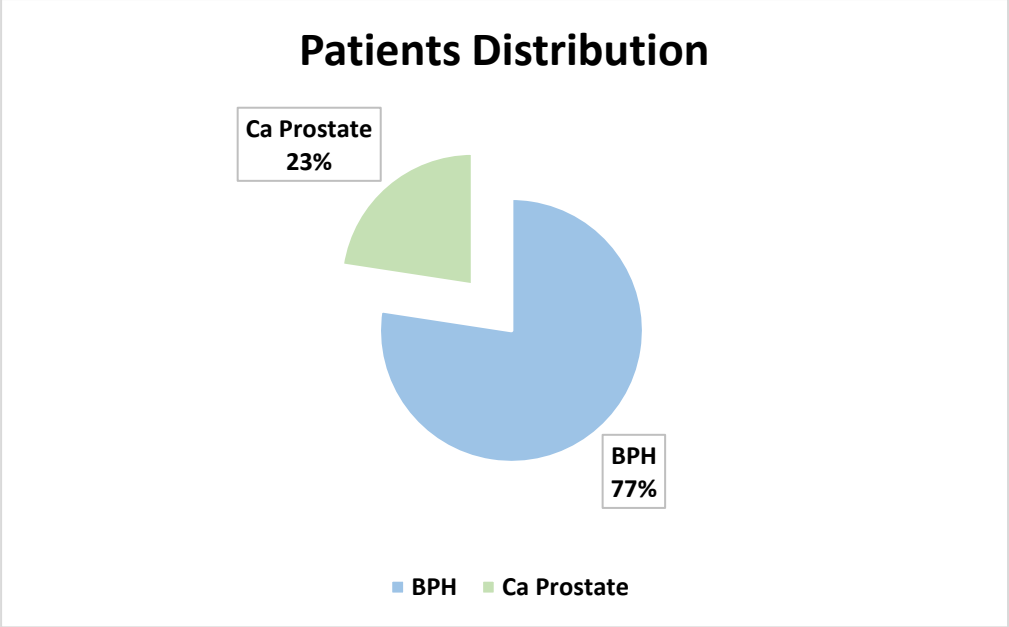


Figure 1: Patient Distribution

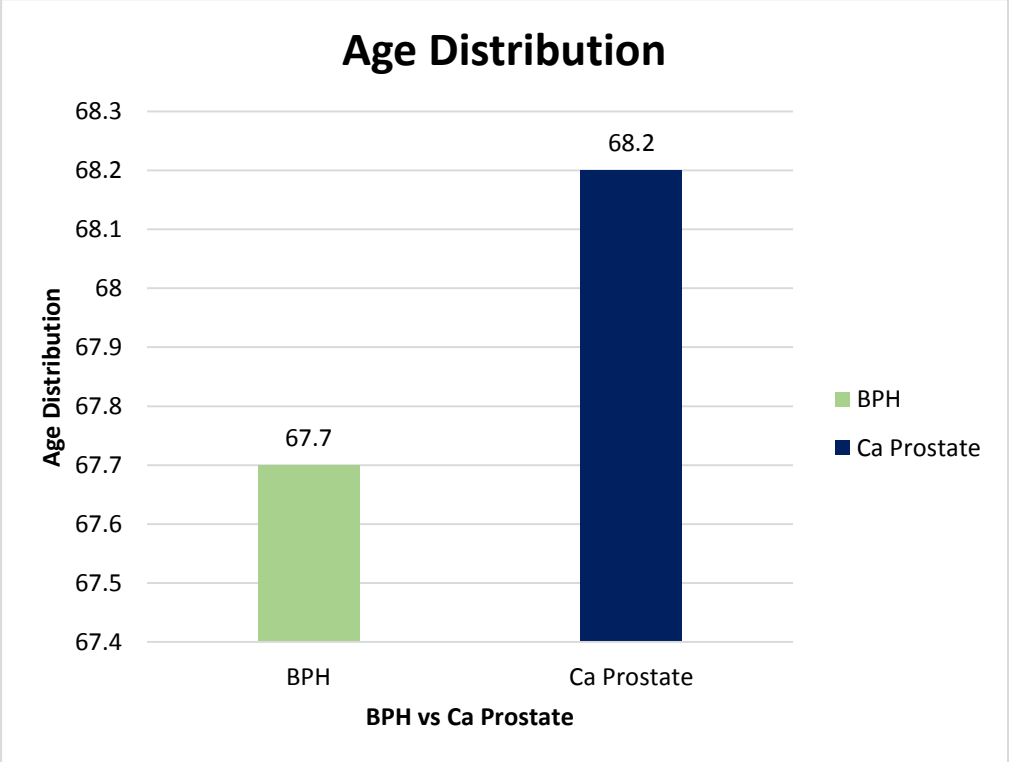


Figure 1a: Patient age Distribution

2. Comparison of Serum PSA

In the BPH group, the median serum PSA values is 6.34 which is significantly lower from the median serum PSA value of patients with carcinoma prostate which is 9.55 (p value 0.016). The appropriate statistical test (non-parametric test - Mann-Whitney U test) has been applied to compare between the groups.

Table 2: Serum PSA

	BPH			**Ca Prostate**			**P value**
Serum PSA (ng/ml)	Median	IQR		Median	IQR		0.016
	6.34	5.03	8	9.55	9	10	

Data in Median (IQR); $ Mann-Whitney U

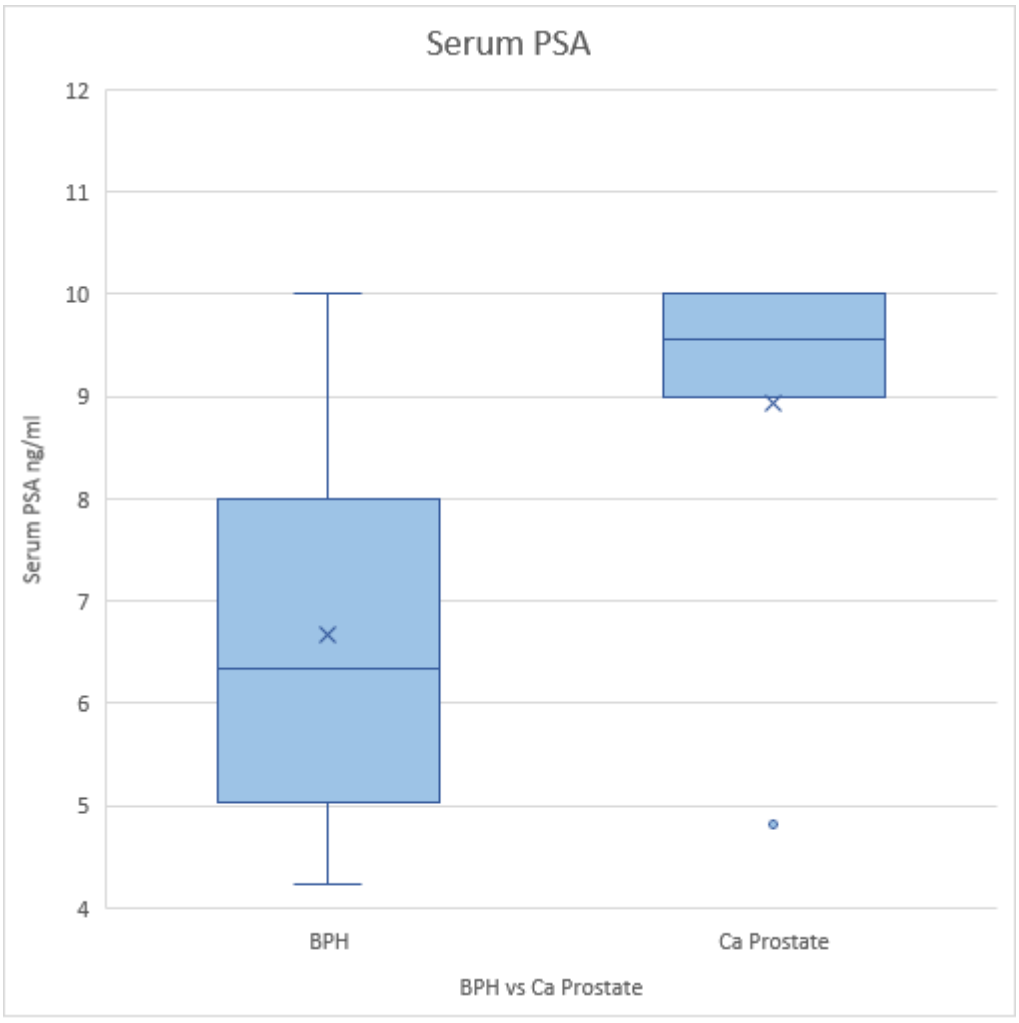


Figure 2: Serum PSA

3. Prostate size

In the BPH group, the median prostate size is 36 grams that is significantly lower from the median prostate size of patients in the carcinoma prostate group which is 67 grams (p value 0.012). The appropriate statistical test (non-parametric test - Mann-Whitney U test) has been applied to compare the data between the groups. Therefore, the prostate size is seen to be much higher in carcinoma prostate patients.

Table 3: Prostate Size

	BPH			**Ca Prostate**			**P value[$]**
Prostate Size (gm)	Median	IQR		Median	IQR		0.012
	36	30.5	46.4	67	43.5	86.5	

Data in Median (IQR); $ Mann-Whitney U

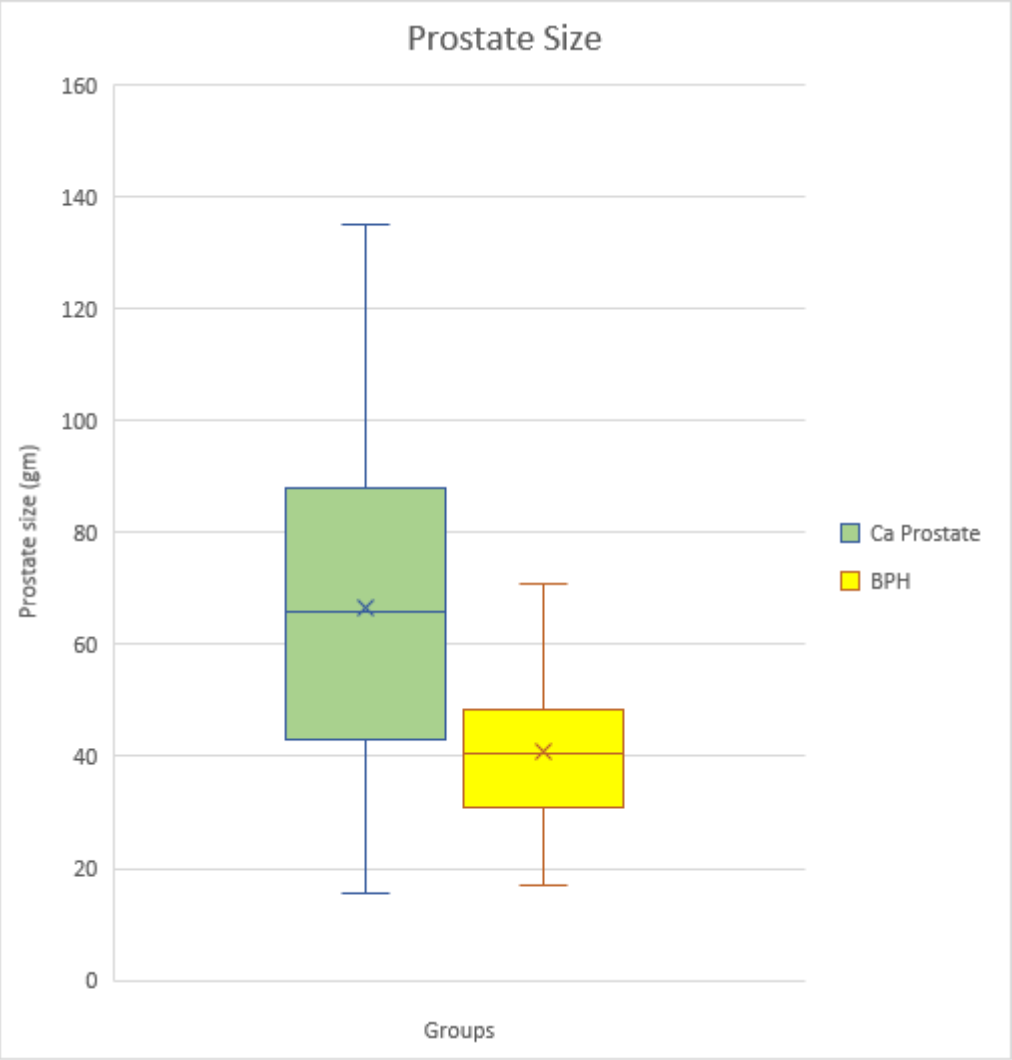


Figure 3: Prostate Size

4. Prostate specific antigen density (PSAD)

Prostate specific antigen density has been compared between the two groups and it was found that the density was higher in carcinoma prostate group and it is significantly lower in BPH patients (p value < 0.05). The appropriate statistical test (non-parametric test - Mann-Whitney U test) was applied to assess the result which showed significant p value.

Table 4: Prostate specific antigen density (PSAD)

	BPH			**Ca Prostate**			**P value**
PSAD (ng/ml^2)	Median	IQR		Median	IQR		0.033
	0.104	0.082	0.131	0.235	0.215	0.3	

Data in Median (IQR); $ Mann-Whitney U

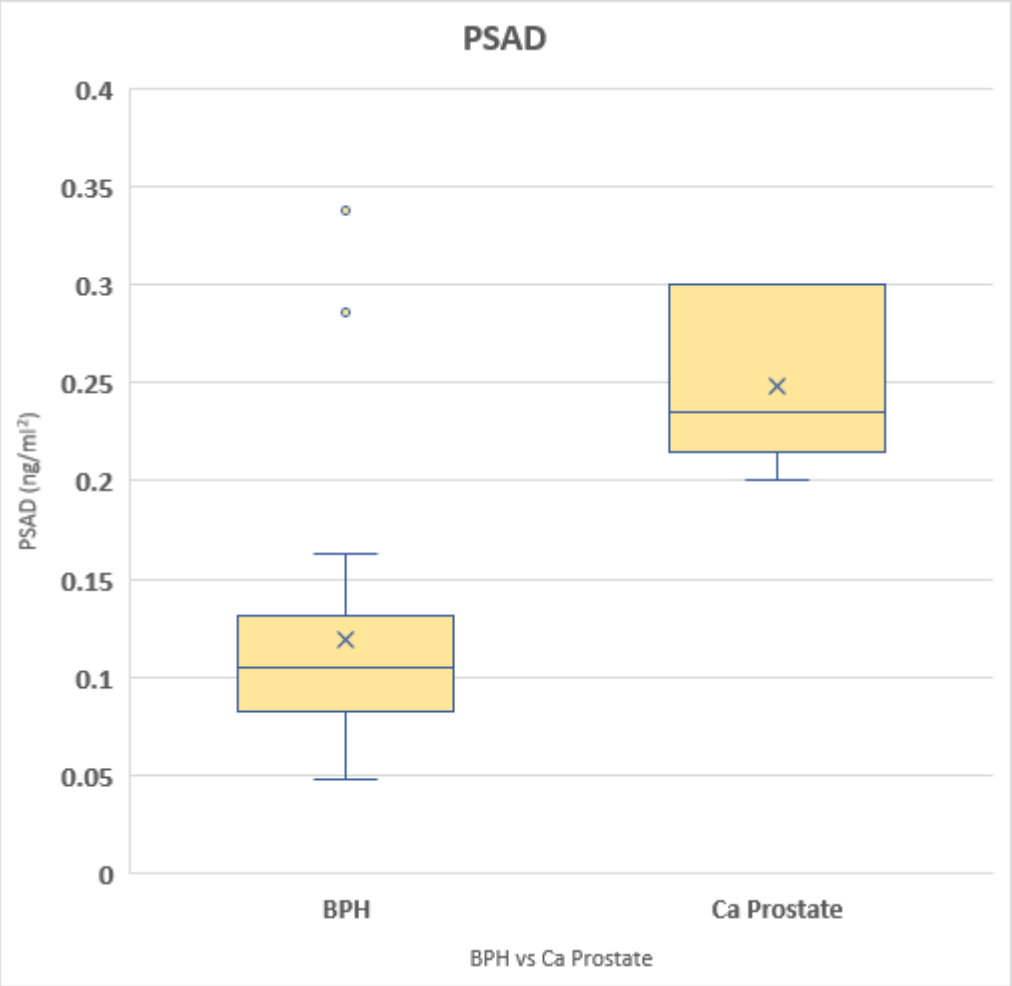


Figure 4: Prostate specific antigen density (PSAD)

5. Change in Urinary PSA

DRE was done in the study population. Change in urinary PSA pre-DRE to post DRE was assessed in both the groups. In the BPH group, the median pre-DRE urinary PSA was 67.7(30.3,196.1) which is significantly lower from the median pre-DRE urinary PSA of patients with carcinoma prostate which is 246.9(66.8,569) with a p value of 0.045. The comparison of post DRE urinary PSA showed no significant difference between the two groups although a higher post DRE urinary PSA was found in BPH patients.

Within the group, comparisons showed a significant change in the pre and post DRE urinary PSA as well. The appropriate statistical test (non-parametric test - Mann-Whitney U test) has been applied to compare between the groups and Wilcoxon sign rank for within the group comparison.

Table 5: Change in Urinary PSA

Ur.PSA	**BPH**			**Ca Prostate**			**P value$**
	Median	IQR		Median	IQR		
Pre-DRE	67.7	30.3	196.1	246.9	66.8	569	0.045
Post-DRE	1048.8	494.2	2259.85	860	315.5	2512	0.085
P value@	0.001			<0.001			

Data in Median (IQR); $ Mann-Whitney U; @Wilcoxon signed-rank test

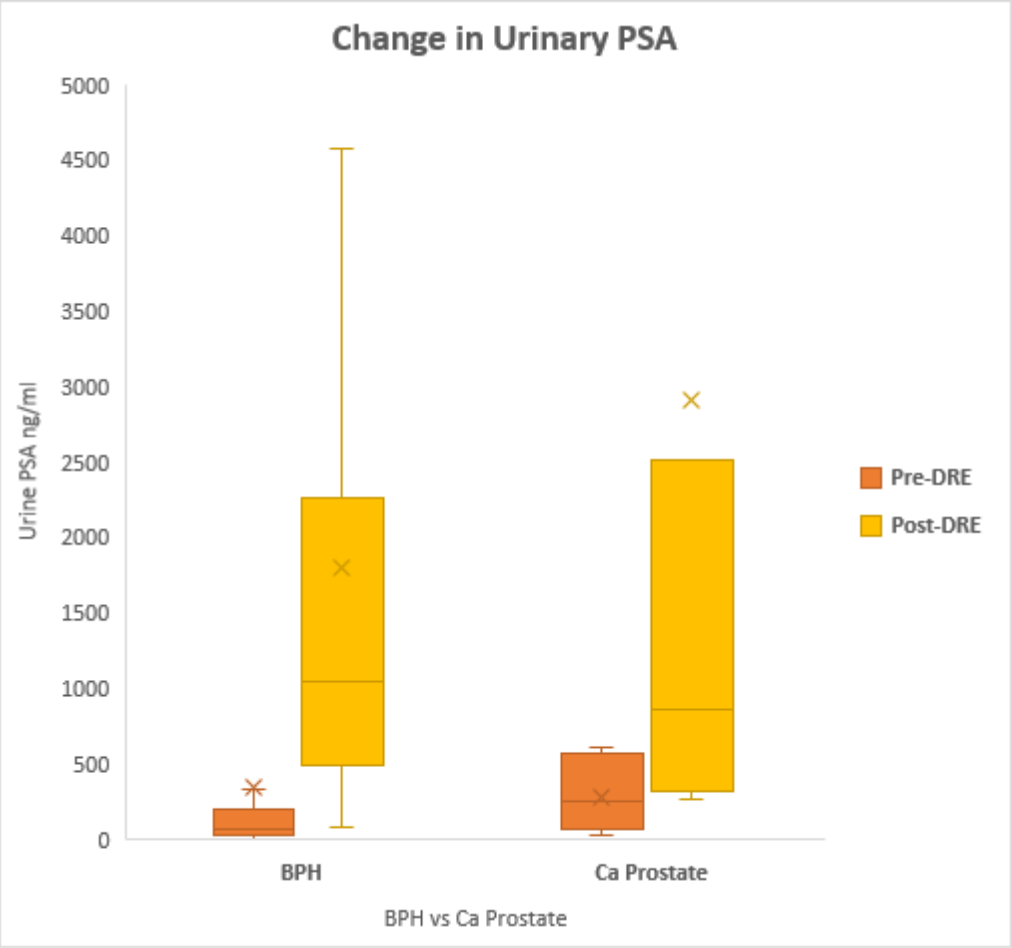


Figure 5: Change in Urinary PSA

6. Ratio of Pre-DRE / Post-DRE Urinary PSA

The ratio of median of pre/post urinary PSA was also assessed between the two groups but there was no significant difference found between the two groups(p=0.256) statistically although significant difference was noted numerically.

Table 6: Ratio of Pre-DRE / Post-DRE Urinary PSA

	BPH			**Ca Prostate**			**P value**
Ratio of change of median value in pre to post DRE Ur. PSA	**15.49**			**3.48**			
Ratio Pre-DRE Ur.PSA / Post-DRE Ur.PSA	Median	IQR		Median	IQR		0.256
	0.072	0.038	0.158	0.548	0.027	0.706	

Data in Median (IQR); $ Mann-Whitney U

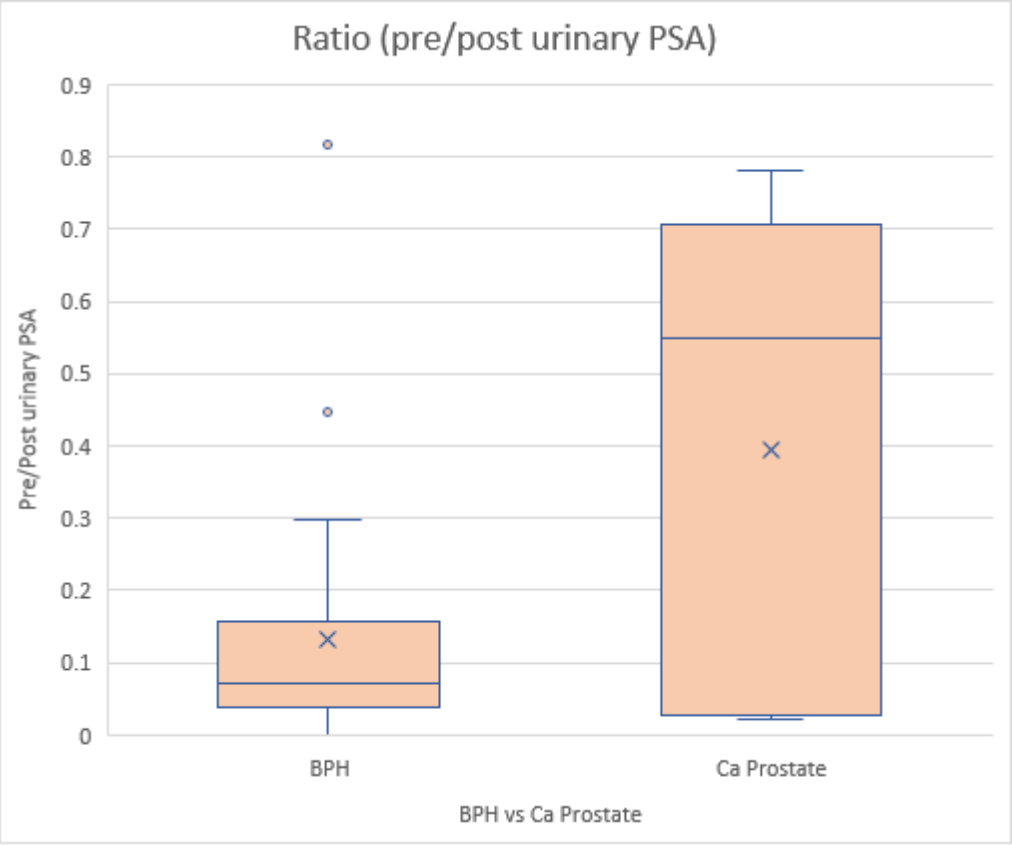


Figure 6: Ratio of Pre-DRE / Post-DRE Urinary PSA

7. Ratio of Pre-DRE Urinary PSA/Serum PSA

The ratio of Pre urinary PSA/S PSA was also assessed between the two groups but there was no significant difference found between the two groups (p=0.295). The ratio was higher in case of carcinoma patients.

Table 7: Ratio of Pre-DRE Urinary PSA/Serum PSA

	BPH			**Ca Prostate**			**P value**
Ratio (Pre-DRE Ur.PSA / Sr.PSA)	Median	IQR		Median	IQR		
	11.434	4.077	29.685	24.914	6.68	63.22	0.295

Data in Median (IQR); $ Mann-Whitney U

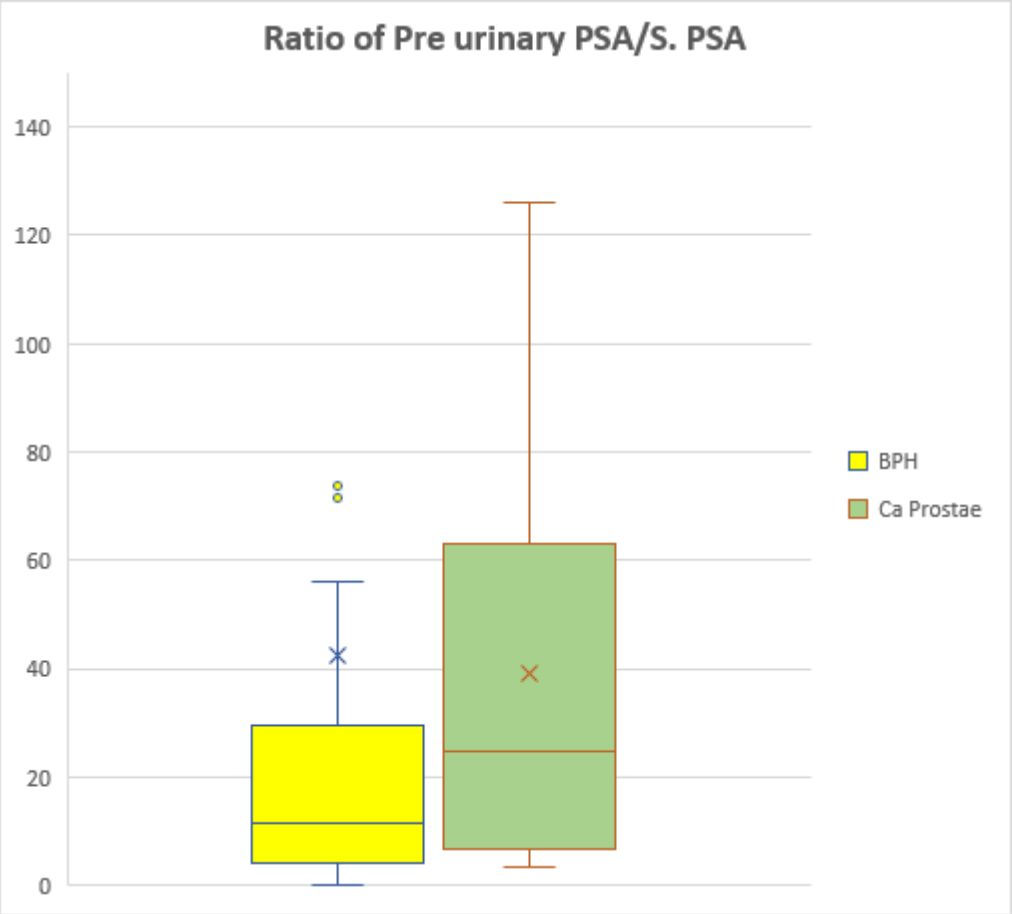


Figure 7: Ratio of Pre-DRE urinary PSA/Serum PSA

8. Ratio of Post-DRE Urinary PSA/Serum PSA

The ratio of Post urinary PSA/ S PSA was also assessed between the two groups but there was no significant difference found between the two groups (p=0.627). The ratio was higher in case of carcinoma patients.

Table 8: Ratio of Post-DRE Urinary PSA/Serum PSA

	BPH			**Ca Prostate**			**P value**
Ratio (Post-DRE Ur.PSA / Sr. PSA)	Median	IQR		Median	IQR		0.627
	176.63	80.84	318.62	99.36	31.85	251.200	

Data in Median (IQR); $ Mann-Whitney U

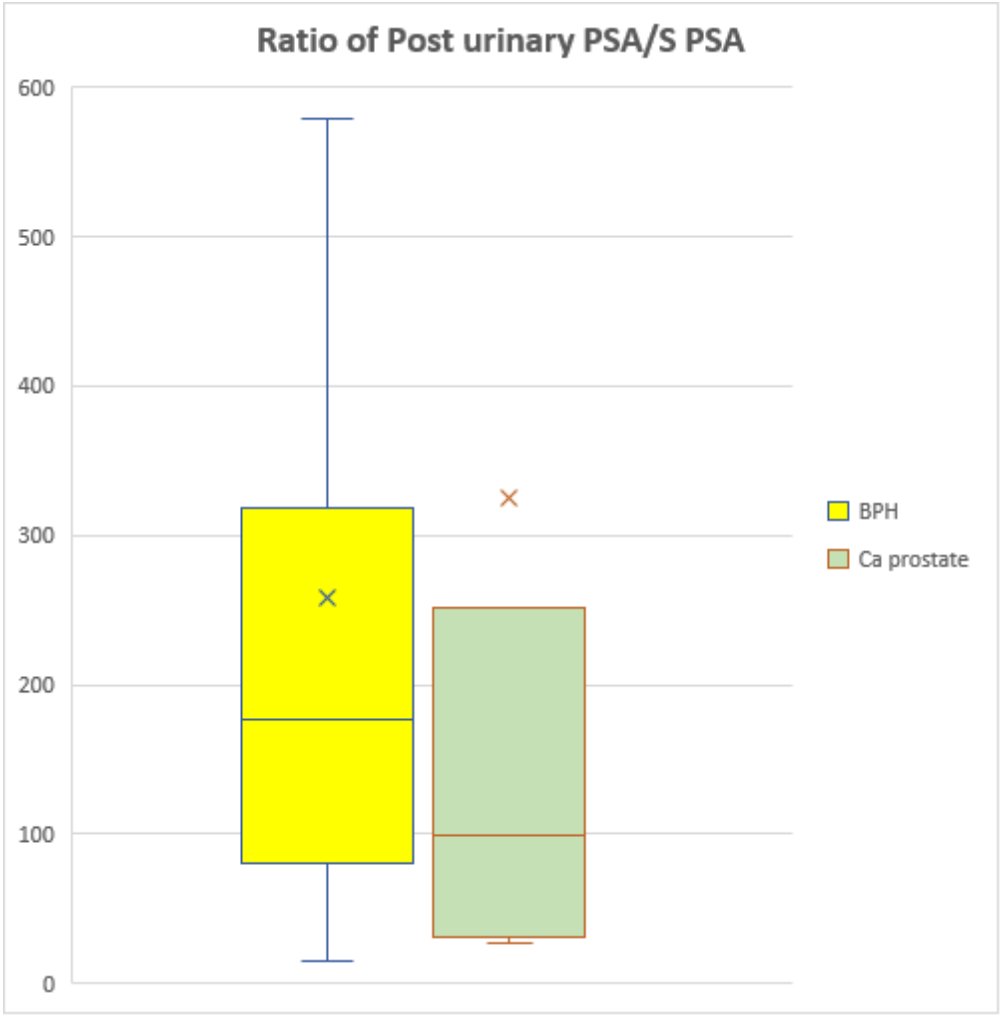


Figure 8: Ratio of Post-DRE Urinary PSA/Serum PSA

9. Regression Analysis

Logistic regression analysis was performed to ascertain the impact of age, sex, serum PSA, prostate size, PSAD on prostate cancer or in patients with BPH. The logistic regression model was statistically not significant for both BPH and prostate cancer groups in terms of age and sex Therefore, we can conclude that serum PSA and PSAD have an impact on the BPH as well as Ca prostate as shown in the below table

Table 9: Regression Analysis

	Variable	B	SE	P value	Exp B	95 % CI	
						Lower	Upper
BPH	**Age**	-2.153	.706	.052	.116	.029	.464
	Sex	-.220	.064	.561	.803	.708	.909
	Serum PSA	.296	.092	.001	1.234	1.123	1.608
	PSAD	-.006	.002	.002	.994	.989	.999
Ca Prostate	**Age**	-2.153	.706	.602	.116	.029	.464
	Sex	-.220	.064	.801	.803	.708	.909
	Serum PSA	.296	.092	.001	1.494	1.123	1.608
	PSAD	-.006	.002	.012	.994	.989	.999

10. Receiver Operating Characteristic Curve (R.O.C Curve) Analysis

Serum PSA (ng/ml)

Receiver operator characteristic (ROC) analysis was performed to detect the cut-off value for the baseline serum PSA levels, to differentiate the patients between BPH and Ca prostate. The cut-off value for baseline serum NSE levels with ROC analysis (AUC=0.804) to differentiate BPH from patients of Ca prostate was found to be 5.21 ng/ml. This value is 85.5% sensitive and 78.3% specific.

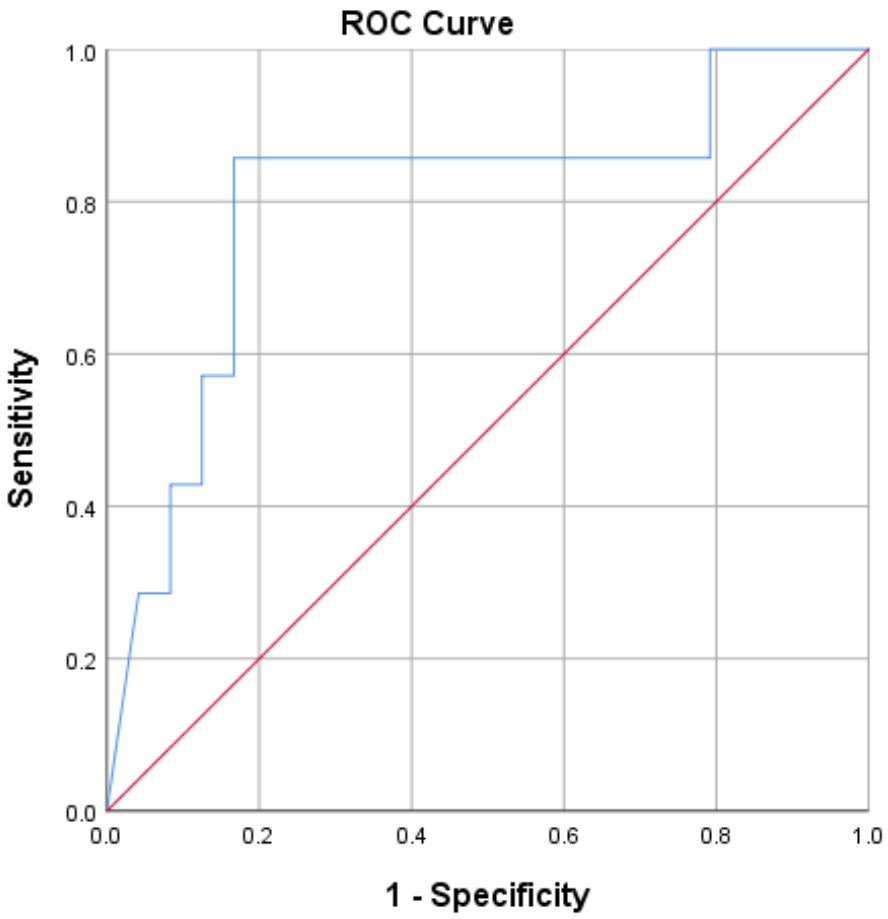


Figure 9: Receiver Operating Characteristic Curve (R.O.C Curve) Analysis

DISCUSSION

This prospective study was conducted in Department of Urology & Kidney Transplant, in both IPD and OPD patients, at Dayanand Medical College & Hospital from March 2020 to February 2021. After clearance from institutional ethical committee and informed written consent, all those patients who fulfilled the criteria were taken up for the study.

Elevated serum prostate specific antigen (PSA) and abnormal digital rectal examination (DRE) are suggestive of Prostate carcinoma. There are certain limitations to serum PSA for diagnosis of Prostate Carcinoma, especially when PSA is between 4 and 10 ng/ml. Patients with and without Prostate carcinoma may have different levels of urine biomarkers such as prostate specific antigen (PSA), glycoproteins and mi RNA. Prostate biopsy is required for a definitive diagnosis of prostate carcinoma, but there is a significant chance of prostate biopsy to be negative when PSA ranges between 4-10ng/ml. Biopsy is an invasive procedure and is associated with several complications.

Chodak et al. and Krahn et al. discussed their respective studies and guidelines about the time to begin PSA screening, which is generally started between 40 and 50 years in high-risk patients, it is still a topic of debate. There are few guidelines suggesting when PSA screening is no longer considered beneficial in view of multiple comorbidities and generally a life expectancy of 10 years or greater is considered before initiating carcinoma prostate screening. [29,30,43,44] In our study none of the participant was included for prostate cancer screening and all the participants were having increased serum PSA with lower urinary tract symptoms.

PSA is not a specific marker for prostate carcinoma because it is also increased by prostatitis, BPH, prostate compression during DRE and endoscopic transurethral surgeries. Prostate carcinoma antigen 3 (PCA3), prostate health index (PHI), sarcosine and other glycoproteins are all the predictors of prostate carcinoma.

Baseline characteristics were evaluated in our study population in which mean age was 67.7 ± 7.2 years and 68.2 ± 8.8 years for BPH group (24 subjects) and the Carcinoma Prostate group (7 subjects) respectively, which is comparable across both the groups. The other parameters at baseline which we assessed were serum PSA, prostate size, pre-DRE-Urinary PSA, post-DRE-Urinary PSA and PSAD. Srivastava et al. in their study on urinary prostate-specific antigen and microseminoprotein-beta levels in patients with and without prostate cancer, had similar population and study design with comparable sample size.[20]

To compare the age distribution of our study, we compared with Cancer Statistics, 2021 reported by Siegel RL et al. which estimates the number of additional cancer cases and fatalities in general population in United States. After comparing, we come across a similar age distribution as in our study.[31] Similar age distribution was also seen by Ferlay J et al. in their study, “Estimates of cancer incidence and mortality in Europe study in 2008”, which was conducted more than a decade ago. [32]

In a report by Bray F et al. “Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries”, they had reported that carcinoma prostate was detected in about 1.27 million new cases worldwide, which makes it the second most common cancer in men.[33]

In our study, the BPH group has median serum PSA values of 6.34 ng/ml which is significantly different from the median PSA value of 9.55 ng/ml in patients with carcinoma prostate (p value 0.016). Our finding is consistent with study by Shrivastava et al. where median PSA values were significantly lower in the BPH group when compared to the Prostate carcinoma group. [20]

In our study, when we analysed the prostate volumes; the median prostate size was 67 grams in BPH group which is significantly higher from the median prostate size of patients with carcinoma prostate i.e.

36 grams (p value 0.012). The appropriate statistical test (non-parametric test - Mann-Whitney U test) has been applied to compare the data between the groups. Therefore, the prostate size is seen to be much higher in BPH patients in our study.

In studies which are showing relationship between serum PSA and PSAD, transition zone has a role in the hypertrophy of an aging prostate due to BPH, but the peripheral zone is thought to be not affected with growing age.[10,45,46] Other than serum PSA, one of the most widely used parameter for diagnosing carcinoma prostate is PSA density (PSAD).[34,35] If we look into the history of PSAD, it has been used to distinguish Prostate carcinoma from BPH since 1992.[36] Contrary to general belief and usual practice, a few previous small studies have also been able to demonstrate that the accuracy of PSAD is superior to serum PSA in predicting Prostate carcinoma as described by Brassell et al. and Benson et al. in their studies on comparison of PSAD and serum PSA levels for detecting Prostate Carcinoma. Prostate specific antigen density has been compared between the two groups in our study and it was found that the PSAD was higher in case of carcinoma prostate (0.235ng/ml^2) group compared to BPH group (0.104ng/ml2) with significant p value of 0.033.

According to previous review articles, PSAD in the prostate transitional zone is much higher in prostate carcinoma patient than in a BPH patient. This translates that if both patients had the same level of serum PSA, the ratio of transitional zone volume to overall amount of prostate volume in Prostate carcinoma patients was less when compared to BPH patients. PSAD has an important role to predict the Gleason score/grade in the prostate biopsy or final specimen of prostatectomy as stated by Ibrahim Karademir et al. and Takash Ohigashi et al. [37,38,39,40] In our study, although PSAD and Gleason score has shown significance, with higher PSAD resulting in higher Gleason score, but this association has very little role to play.

DRE was done in all the patients. The change in urine PSA before and after DRE was assessed. In the BPH group, the median pre-DRE urine PSA was 67.7 ng/ml which was significantly different from the median pre-DRE urine PSA of patients with carcinoma prostate (246.9 ng/ ml) with a p value of 0.045. The comparison of post DRE urine PSA showed no significant difference between the two groups. Analysing urinary PSA values in BPH group, it showed a significant change in pre to post DRE urinary PSA. The appropriate statistical test (non-parametric test - Mann-Whitney U test) has been applied between the groups to analyse the data and within the group, it was done using Wilcoxon sign rank test. In our study, pre-DRE urine PSA was higher in Prostate Carcinoma patients when compared to BPH which is contrary to results as per Bolduc et al. In their study, the sensitivity of Pre-DRE urinary PSA value of less than 150 ng/ml in diagnosing carcinoma prostate was 92.5% thereby reducing the number of prostate biopsies.[15]

Our findings of increased post-DRE urinary PSA in patients without Prostate carcinoma compared to pre-DRE samples are consistent with study findings of Prashant Shrivastava et al. In their study, more prominent differences were seen in the BPH group than in the Prostate carcinoma group.[20] The specific mechanism behind this phenomenon is still unknown, but it is believed that prostate gland's cellular architecture is preserved with undamaged cell membrane and ductal structure resulting in expression of prostatic secretion into the urethra. Proteins and other molecules/exosomes thus, secreted into the urethra through the undamaged ducts as a result of prostate manipulation. Whereas, in carcinoma prostate normal prostatic architecture is lost, resulting in secretion of PSA into blood stream across the basement membrane, thus resulting in an increased PSA level in blood as well as in urine but prostatic manipulation in Prostate Carcinoma may not release equivalent urinary PSA when compared to BPH. Hence, explaining more rise in urinary PSA after DRE in males without Prostate carcinoma as stated by Pejcic Tet al.[28]

Also, the ratio of change of median pre-DRE to post DRE urinary PSA in BPH (15.49) and carcinoma prostate (3.48) was calculated in both the groups which was significant numerically. Though the differences between the groups were not statistically significant. The changes in the urine PSA values were much higher in the BPH patients when compared to the carcinoma prostate patient group.

The ratio of pre-DRE to post DRE urinary PSA was also evaluated between the two groups of patients with BPH and carcinoma prostate, but there was no statistically significant difference found between the two groups (p=0.256). The ratio of Pre DRE urinary PSA to S.PSA and Post DRE urinary PSA to S.PSA was also assessed between the two groups but there was no significant difference found.[18] This is contrary to study by Irani J et al. in which the ratio of serum to urinary PSA showed significant difference in differentiating BPH from carcinoma prostate.

Borghesi M et al. studied and discussed about complications of prostate biopsy after TRUS guided biopsy, trans perineal and MRI guided prostate biopsy in their study "Complications After Systematic, Random, and Image-guided Prostate Biopsy". Most of the complications were minor and self-limiting and doesn't require hospitalization except for very few in which post biopsy infections or sepsis occurred. In our study, no major complication occurred except for minor per rectal bleed or mild hematuria.[41]

Many laboratory and imaging approaches are widely employed in the early detection of carcinoma prostate; however prostate biopsy is still the gold standard for diagnosis. Iwakiri J et al., in their study, "An analysis of urinary prostate specific antigen before and after radical prostatectomy: evidence for secretion of prostate specific antigen by the periurethral glands", evaluated the importance of first voided and mid-stream, pre and post DRE urinary PSA in patients after radical prostatectomy and cystoprostatectomy. In our study, we also collected

first voided urinary sample, before and after DRE for the measurement of urinary PSA. [42]

To evaluate and to calculate the probability of occurrence of binary event occurring, logistic regression was performed to ascertain the effects of age, sex, serum PSA, prostate size, PSAD on prostate cancer as well as BPH. The logistic regression model was statistically not significant for both BPH and prostate cancer in the present population and present data set. Therefore, we can conclude that serum PSA and PSAD have an impact on the BPH as well as Ca prostate as shown in the results.

A ROC curve analysis was done to distinguish between BPH and Prostate carcinoma. The cut-off value for baseline serum PSA levels was determined using receiver operator characteristic (ROC) analysis to distinguish patients with BPH and Ca prostate. With ROC analysis (AUC=0.804), the cut-off value for baseline NSE levels to distinguish BPH from those with Ca prostate was found to be 5.21 ng/ml. This number has a sensitivity of 85.5 percent and a specificity of 78.3 percent.

As our study had 31 patients which include 24 patients of BPH of 7 patients of carcinoma prostate. The sensitivity and specificity of urinary PSA in our study could have been increased if the number of participants were more.

SUMMARY

The present study is a prospective observational study conducted in both IPD and OPD patients in the department of Urology & Kidney Transplant at Dayanand Medical College & Hospital from March 2020 to February 2021.

- The study was aimed to determine the association of urinary PSA in differentiating benign prostate hyperplasia from carcinoma prostate particularly when serum PSA is in equivocal range.
- After clearance from institutional ethical committee and informed written consent, all those patients who fulfill the criteria were taken up for this study.
- The median serum PSA values in BPH and carcinoma prostate groups were 6.34 ng/ml and 9.55 ng/ml respectively which is significantly different with a p value of 0.016.
- Prostate specific antigen density has been compared between the two groups and it was found that the density was higher in case of carcinoma prostate and significantly lower in case of BPH patients (p value < 0.05).
- The ratios of median of pre-DRE to post DRE urinary PSA in BPH group (15.49) and carcinoma prostate group (3.48) were calculated which was significant. The ratios of pre-DRE urinary PSA to post DRE urinary PSA, Pre DRE urinary PSA to serum PSA and Post DRE urinary PSA to serum PSA were also assessed within the two respective groups but there was no significant difference found between the two groups.
- Our findings of higher post-DRE urinary PSA compared to pre-DRE samples were more prominently seen in the BPH group than in the carcinoma prostate group.
- A ROC curve analysis was done to distinguish between BPH and Prostate Carcinoma. The cut-off value for baseline serum PSA levels was determined using receiver operator characteristic (ROC) analysis (AUC=0.804) to distinguish

patients with BPH and Ca prostate and it was found to be 5.21 ng/ml. This value has a sensitivity of 85.5 percent and a specificity of 78.3 percent which is less when comparing to the study by Bolduc el al. In their study, the sensitivity of Pre-DRE urinary PSA value (< 150 ng/ml) in diagnosing carcinoma prostate was 92.5%.

CONCLUSION

To conclude our study was able to demonstrate the role of urinary pre-DRE and post- DRE PSA in distinguishing between benign prostate hyperplasia and prostate cancer. The change in median pre-DRE urinary PSA to Post DRE urinary PSA is about 4.45 times more in BPH group when compared to carcinoma prostate group. Although it is numerically significant but statistically it is insignificant as it is a median value.

Clinical prediction, on the other hand, continues to be problematic. As a result, more studies are needed to corroborate the conclusion of our study.

LIMITATIONS

- The results would have been better appreciated if the number of participants were more.
- Further as in this study only TRUS was used to guide the biopsy, a more favorable result could be achieved if MRI guided or MRI TRUS fusion biopsies were taken.

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PROFORMA

Sr No._____

Name_____ Age_____

MRD_____

C/O_____

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HOPI_____

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Pasthistory_____

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PersonalHistory_____

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Other significant history_____

Signature of Candidate **Signature of Supervisor**

General physical examination

P/A

DRE

Signature of Candidate **Signature of Supervisor**

INVESTIGATION

Hb TLC PLT

Sr Urea Sr Creatinine Coagulation profile (PTI/INR)

Urine Examination (routine and culture)

Ultrasonography- KUB and prostate……..

Serum prostatic specific antigen……..

Urine prostate specific antigen:

Pre DRE	Post DRE

Histopathology Report:

Signature of Candidate **Signature of Supervisor**

KEY TO MASTERCHART

MRD NO.	Medical Record Department Number
DRE	Digital Rectal Examination
S. PSA	Serum Prostate-Specific Antigen
PTI/INR	Prothrombin Time/International Normalized Ratio
PSAD	Prostate-Specific Antigen Density
PB	Prostate Biopsy

Sno.	Name	Age(yrs)	MRD	DRE	Urine examination	S.PSA	PTI/INR	Prostate size	Pre DRE Urinary PSA	Post DRE Urinary PSA	Ratio (pre/post urinary PSA)	Ratio Pre urinary PSA/S.PSA	Ratio Post urinary PSA/S.PSA	PSAD	Biopsy report	Major complication after PB
1	RKS	64	988690	normal	Sterile	9.27	10.7/0.98	70	2.34	557	0.0042	0.2524	60.0863	0.1324	BPH	nil
2	SB	68	984805	normal	Sterile	6.7	11.2/1.03	82	1.06	100	0.0106	0.1582	14.9254	0.0817	BPH	nil
3	RS	58	1019427	normal	Sterile	9.98	14.5/1.33	68	27.46	327	0.0840	2.7515	32.7655	0.1468	BPH	nil
4	AKJ	57	245644	normal	Sterile	6	11.4/1.05	45	282	1680	0.1679	47.0000	280.0000	0.1333	BPH	nil
5	KLS	73	417527	normal	Sterile	6.85	10.4/0.95	42	30.1	1394	0.0216	4.3942	203.5036	0.1631	BPH	nil
6	HS	74	1052107	normal	Sterile	4.43	11.3/1.06	36	15.34	85	0.1805	3.4628	19.1874	0.1231	BPH	nil
7	JS	65	1042814	suspicious	Sterile	5.54	12.6/1.23	46	70	85.65	0.8173	12.6354	15.4603	0.1204	BPH	nil
8	SP	55	861393	normal	Sterile	4.53	11.1/1.02	76	325	1096	0.2965	71.7439	241.9426	0.0596	BPH	nil
9	VK	59	1122044	normal	Sterile	8	16/1.3	28	35	825	0.0424	4.3750	103.1250	0.2857	BPH	nil
10	JK	82	1149977	normal	Sterile	7.37	11.9/1.06	88	86	1254	0.0686	11.6689	170.1493	0.0838	BPH	nil
11	KRS	57	687223	normal	Sterile	5	12/1.1	65	56	925	0.0605	11.2000	185.0000	0.0769	BPH	nil
12	BS	64	624730	normal	Sterile	4.5	13.4/1.26	48	120	480	0.2500	26.6667	106.6667	0.0938	BPH	nil
13	KSJ	70	1130472	suspicious	Sterile	6.47	14.3/1.3	135	0.52	520	0.0010	0.0804	80.3709	0.0479	BPH	nil
14	SL	78	1132526	suspicious	Sterile	5.3	13.6/1.16	15.7	296.5	3069.6	0.0966	55.9434	579.1698	0.3376	BPH	nil
15	AS	73	156877	suspicious	Sterile	6.07	15/1.23	127	186.3	1766.9	0.1054	30.6919	291.0873	0.0478	BPH	nil
16	DS	70	1146644	normal	Sterile	8.27	14.6/1.06	65	199.4	4569.2	0.0436	24.1112	552.5030	0.1272	BPH	nil
17	SSP	70	1125381	normal	Sterile	10	13.9/1.08	98	5717	12761	0.4480	571.7000	1276.1000	0.1020	BPH	nil
18	JS	64	1170420	normal	Sterile	4.23	11.1/1.02	43	312.5	2416.8	0.1293	73.8771	571.3475	0.0984	BPH	nil
19	AB	63	75141	normal	Sterile	6.21	14.8/1.19	66	96.4	1001.6	0.0962	15.5233	161.2882	0.0941	BPH	nil
20	FH	68	987522	suspicious	Sterile	9.77	10.5/0.97	88	65	1789	0.0363	6.6530	183.1116	0.1110	BPH	nil
21	GS	66	1137707	suspicious	Sterile	5.13	12.5/1.09	42	36.5	485.6	0.0752	7.1150	94.6589	0.1221	BPH	nil
22	VK	59	1122044	normal	Sterile	8	11.7/1.07	88	35	658.2	0.0532	4.3750	82.2750	0.0909	BPH	nil
23	S	76	626258	normal	Sterile	7.77	12.5/1.21	72	30.91	2547	0.0121	3.9781	327.7992	0.1079	BPH	nil
24	PN	81	1141892	normal	Sterile	4.77	13.5/1.16	71	126	2654	0.0475	26.4151	556.3941	0.0672	BPH	nil
25	SL	70	994706	normal	Sterile	9.22	11.7/1.07	36	323	14700	0.0220	35.0325	1594.3601	0.2500	ADENO CA(3+4)	nil
26	JPG	78	221628	suspicious	Sterile	10	11.5/1.05	46.4	66.8	2512	0.0266	6.6800	251.2000	0.2200	ADENO CA(3+3)	nil
27	LS	60	1139828	suspicious	Sterile	9	11.1/1.02	45	569	894.3	0.6363	63.2222	99.3667	0.2000	ADENO CA (3+4)	nil
28	JS	78	1160830	suspicious	Sterile	9.91	12.6/1.15	30	246.9	315.7	0.7821	24.9142	31.8567	0.3000	ADENO CA(4+3)	nil
29	RL	73	259913	normal	Sterile	10	11.3/1.03	33	145.6	265.5	0.5484	14.5600	26.5500	0.3000	ADENO CA(3+4)	nil
30	JS	55	1197443	suspicious	Sterile	9.55	12/1.1	49.2	31.51	858	0.0367	3.2995	89.8429	0.2200	ADENO CA (3+3)	nil
31	RKB	67	1177066	suspicious	Sterile	4.82	11.9/1.09	17	606.92	860	0.7057	125.9170	178.4232	0.2000	ADENO CA(3+3)	nil

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Date 5/8/2021

The Principal,
DMC, Ludhiana

Subject: Approval of Plan of Thesis.

This is to inform you that the Faculty of Medical Sciences in its meeting held on 22.01.2021 has approved the plan of thesis of Dr Vivek Gorka, a student of your college for MCh Urology along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis
Evaluating the role of urinary psa in differentiating benign prostate hyperplasia from carcinoma prostate

Supervisor
Dr. Arvind Goyal
Assoc. Prof.,
Dept. of Urology,
DMCH, Ludhiana.

Co-Supervisor
Dr. Sandeep Sharma
Prof. & Head,
Dept. of Urology,
DMCH, Ludhiana.

Dr. Navjot Bajwa
Prof. & Head,

The student has to submit the three copies of thesis (along with PDF format) , to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She must directed to attach a photocopy of this letter with the forwarding letter while submitting thesis to the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic,(if any).

Dr. S P Singh MS(Oph)
Controller of Examinations

Note :

17. *If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.*

EVALUATING THE ROLE OF URINARY PSA IN DIFFERENTIATING BENIGN PROSTATE HYPERPLASIA FROM CARCINOMA PROSTATE

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

MCh

IN

UROLOGY

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES

FARIDKOT

MARCH, 2020

DR. VIVEK GORKA

DEPARTMENT OF UROLOGY

DAYANAND MEDICAL COLLEGE & HOSPITAL

LUDHIANA

ABSTRACT OF PLAN OF THESIS

Title	EVALUATING THE ROLE OF URINARY PSA IN DIFFERENTIATING BENIGN PROSTATE HYPERPLASIA FROM CARCINOMA PROSTATE
For the degree of	MChUrology
Name of the candidate	Dr.VivekGorka
Supervisor	Dr. ArvindGoyal, Associate professor, Department of urology, DMCH, Ludhiana
Co-supervisor	Dr. Sandeep Sharma, Professor & Head, Department of Urology, DMCH, Ludhiana DrNavjotBajwa, Professor & Head, Department of Biochemistry, DMCH, Ludhiana
Institution	Dayanand Medical College & Hospital, Ludhiana
University	Baba Farid University of Health Sciences, Faridkot

Introduction:PSA is a well known marker for carcinoma prostate. But it is seen very occasionally that when serum PSA is in equivocal range associated with no findings on DRE,UrinaryPSA has also its role in differentiating carcinoma prostate from BPH.

Aim of Study:1.To determine the association of urinary PSA in differentiating benign prostate hyperplasia and carcinoma prostate.

2. To study its role in diagnosis carcinoma prostate in cases when serum PSA is in equivocal range.

Materials & Methods:After clearance from institutional ethical committee and informed written consent from all those patients who fulfill the criteria will be taken up for the study. A urine sample before digital rectal examination and immediately after will be collected for urinary PSA level.

Clinical Significance:We will be able to limit the number of prostate biopsies when the S. PSA is in equivocal range after studying this set of population.

Keywords: serum prostate specific antigen, prostate carcinoma, digital rectal examination, transrectal ultrasonography.

(Signature)	(Signature)	(Signature)	(Signature)	(Signature)
Candidate	Co-supervisor	Co-supervisor	Supervisor	Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"EVALUATING THE ROLE OF URINARY PSA IN DIFFERENTIATING BENIGN PROSTATE HYPERPLASIA FROM CARCINOMA PROSTATE"** exist in the Department of Urology, DMC&H, Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis is genuine and is collected by the candidate himself/herself under our supervision and guidance.

Supervisor

Dr. ArvindGoyal
Associate Professor
Department of Urology
DMCH, Ludhiana

Co-Supervisors

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Place : _____

Date : _____

APPROVAL PROFORMA
BYRESEARCH & ETHICAL COMMITTEE
DAYANAND MEDICAL COLLEGE & HOSPITAL, LUDHIANA

Name of candidate	Dr.VivekGorka
Department	MChUrology
Topic of Thesis	EVALUATING THE ROLE OF URINARY PSA IN DIFFERENTIATING BENIGN PROSTATE HYPERPLASIA FROM CARCINOMA PROSTATE
Likely date of appearing in PG examination	MAY, 2022
Date of enrollment	11th September, 2019
Name of Head of Department	Dr.Sandeep Sharma
1) Supervisor **2) Co-Supervisor(s)**	Dr. Arvind Goyal Dr. Sandeep Sharma Dr. Navjot Bajwa
Signature of Members of Research Committee with Stamp	**Signature of Members of Ethics Committee with Stamp**
Dr. Jaspal Singh (Professor & Head, Surgery)	Mr. A K Jindal (Member, Ethics Committee)
Dr. Dinesh Gupta (Professor & Head, Medicine)	Dr. Anu Sharma (Professor, Anatomy)
Dr. SandeepKaushal (Assistant Dean Academics)	Dr. Deepinder K Chhina (Professor & Head, Microbiology)
Dr. Rajoo Singh Chhina (Dean Academics)	Dr. NeenaSood (Professor & Head, Pathology)
Dr. Gurpreet S Wander (Vice Principal)	Dr. Gurpreet S Wander (Vice Principal)
	Dr. Gagandeep Singh (Secretary, Ethics Committee Professor & Head, Neurology)

Approved: Yes /~~No~~

Dr. SandeepPuri
Chairperson
Research Committee

Chairperson
Research Committee

Approved: Yes /~~No~~

Prof. ArvindMalhotra
Chairperson
Ethics Committee

Chairperson
Ethics Committee

BABA FARID UNIVERSITY OF HEALTH SCIENCES, FARIDKOT

PROFORMA FOR REGISTRATION OF SUBJECT FOR DISSERTATION

1	NAME OF THE CANDIDATE AND ADDRESS	Dr. Vivek Gorka H. No 117, Ward-5, Bishnah Jammu J & K-181132
2	NAME OF THE INSTITUTE	DAYANAND MEDICAL COLLEGE AND HOSPITAL, LUDHIANA
3	COURSE OF STUDY AND SUBJECT	MCh UROLOGY
4	DATE OF ADMISSION INTO THE COURSE	11th September, 2019
5	TITLE OF THE TOPIC	EVALUATING THE ROLE OF URINARY PSA IN DIFFERENTIATING BENIGN PROSTATE HYPERPLASIA FROM CARCINOMA PROSTATE

6. BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

PSA (Prostate Specific Antigen) is a serine protease and is produced by the epithelial cells of prostatic tissue, both benign and malignant. Physiologically, it is present in the seminal fluid at high concentration and it's function is to cleave the high molecular weight proteins responsible for the seminal coagulum into smaller polypeptides. This action results in liquefaction of the coagulum. PSA is also present in the serum and can be measured reliably by either a monoclonal immunoradiometric assay or a polyclonal radioimmunoassay. The calculated half-life of serum PSA ranges from 2.2 to 3.2 days and the metabolic clearance rate of this tumor marker follows first-order kinetics. Digital rectal examination, cystoscopic examination and prostate biopsy all can cause spurious rise in serum PSA concentration. Conditions such as bacterial prostatitis and acute urinary retention also increases the serum PSA level. Approximately 25% of the patients with BPH will have mildly raised serum PSA concentration in blood.[1]

PSA was discovered and published in the Journal of Reproduction and Fertility and in the Journal of Immunology as early as in 1970 in USA. Biochemically, PSA in seminal fluid is present in free form has a molecular weight of about 30,000 daltons, while in serum, where it is complexed with alpha1-chymotrypsin and other proteins, its molecular weight is approximately 100,000 daltons being comparable to that of prostatic acid phosphatase.[2]

Serum prostatic specific antigen (PSA) has proven to be a generally reliable indicator in the diagnosis and management of prostate cancer. Abnormal findings on digital rectal examination associated with increased serum prostate specific antigen level is confirmed by prostatic biopsy. Serum PSA has revolutionized the management and follow-up of prostate cancer.[3,4]

Multiparametric MRI is a non-invasive tool for diagnosing carcinoma prostate but it has its own limitations such as high cost, limited availability, errors in interpretations[5]

There are many non-invasive modalities including biomarkers in serum, urine, semen such as DNA, RNA, proteins for diagnosing carcinoma prostate.[6]

Digital rectal examination results in the drainage of prostatic secretions; thus, urinary sample after digital rectal examination of prostate results in expulsion of its secretions into urethra and hence, large amount of prostatic secretions will be present in the urine.[7]

There is still very little literature about the possible role of urinary PSA in the diagnosis or follow-up of prostate cancer. All cancers diagnosed on biopsy are not aggressive and need treatment. Thus, a biopsy showing clinically insignificant cancer may not require treatment or a biopsy may miss a significant cancer that would require treatment otherwise. Therefore, the aim of our study is to evaluate the usefulness of urinary PSA in the differential diagnosis between benign prostatic hyperplasia (BPH) and prostate cancer, especially when serum PSA is equivocal.

6.2 REVIEW OF LITERATURE

Prostate cancer is the second most common cause of cancer death in males. Serum PSA remains the single best test for the detection of early prostate cancer and multiple variations have been studied to improve its sensitivity and specificity, first by associating it with the digital rectal examination and then by looking at the age-adjusted PSA, PSA density, PSA velocity and percent free PSA. The upper limit of normal PSA (4.0 ng/ml) can also be lowered to 2.5 ng/ml because 20%–30% of tumors will be missed if the only method of detection is serum PSA with a cut off of 4.0 ng/ml.[8]

Serum PSA is the most widely used screening test for prostate cancer (Pca) and any increase in serum PSA is considered to be the main cause of the stage migration recently observed. The ratio of free to total serum PSA (%FPSA) has been shown to increase PSA accuracy in cancer detection; however, few screening studies have systematically evaluated its role in cancer detection rates in men with PSA levels <4.0 ng/ml and normal DRE.[9]

Although Pca screening is widely utilized nowadays; but two thirds of the biopsies performed are still unnecessary. Thus, the discovery of non-invasive Pca biomarkers remains necessary. In recent years, the utilization of urine as a non invasive Pca biomarker has emerged as an attractive option for detection of Pca.[10]

Serum Prostate-specific antigen (PSA) is the single most important tumor marker which is used in early detection and monitoring of prostate cancer (PCa). However, routine analysis of serum PSA concentrations does not allow differentiation between Pca and prostatic diseases. Determination of the serum-to-urinary PSA ratio enhances the specificity of PSA in screening of Pca and monitoring of patients with Pca under androgen deprivation therapy.[11]

Benign prostatic hyperplasia (BPH) was associated with significantly higher urine levels of prostate-specific antigen (PSA) than in prostate cancer. Thus, serum/urine PSA ratio (PSA S/U) will help in patients for the differential diagnosis of Pca, particularly when the pre-biopsy serum level of PSA lies between 4.0 and 10.0 ng/ml.[12]

Expressed prostatic secretions represents the fluid being secreted by the prostate following a digital rectal prostate massage, which in turn can be collected in voided urine post-examination.[7]

Of all PSA-based markers, only the FDA-approved prostate health index (phi) shows improved specificity over percent free PSA (%fPSA) and total PSA. In urine, the FDA-approved prostate cancer gene 3 (PCA3) has also proven its utility in the detection and management of early PCa with advantages as compared with PSA and %FPSA.[13]

The role of urinary proteomics in the diagnosis of prostate cancer is undefined. Levels of urinary biomarkers such as prostate-specific antigen and PCA3 may differ between men with and without Pca.[14]

The cancer detection rate with 16-core TRUS-guided biopsy is significantly higher than that with 10-core biopsy (54.76% vs. 15.09%, $p<0.001$). In patients with both normal and abnormal DRE findings, 16-core biopsy has a better detection rate than the 10-core biopsy protocol.[15]

In some cases, however, urine PSA levels can be elevated in men with local tumor recurrence after Radical Prostatectomy (RP) when serum levels are still undetectably low. This indicates that the determination of urinary PSA concentration might be useful in the follow-up of patients after RP.[16,17,18]

Tremblay et al studied the mode of excretion of three prostatic secretory proteins, namely acid phosphatase (PAP), prostate-specific antigen (PSA) and beta-inhibin, in the urine of normal adult men which showed that PAP concentrations in 50% of men with or without symptomatic BPH were similar to those of normal young men. In the remaining 50%, PAP was undetectable. In contrast, average PSA and beta-inhibin concentrations were higher in patients with BPH than in young men (p less than 0.05). The three markers were decreased or nondetectable in about half of the patients with untreated prostatic cancer.[19]

Ravery et al concluded that cancer secretes more serum PSA per volume than benign prostatic hyperplasia. PSA density (PSAD, serum PSA divided by the volume of the entire prostate) has been suggested

as an additional diagnostic criterion. In 153 men with prostatism and PSA values between 4 and 10 ng/ml (Hybritech assay), the volume of the prostate was determined by transrectal ultrasonography and 6 systematic biopsies were taken. The groups with positive and negative biopsies respectively were compared according to age of the patient, results of DRE and PSAD. Histological grade of positive biopsies and pathological stage of patients who underwent radical prostatectomy were also compared with diagnostic criteria. Prostate cancer was found in 45 of 153 men (29.4%). Patient's age had no influence on detection rates. The positive predictive value of a PSAD of 0.2 or more was twice the value of a PSAD below 0.2, irrespective of DRE findings. An increasing number of positive biopsies was associated with increasing PSAD and histological grade.[20]

Robert G Uzzo et al studied role of percent free PSA in men with a total PSA between 2 and 4 ng/mL. Men with a normal DRE and total PSA between 2 and 4 ng/mL were advised to undergo transrectal ultrasound-guided (TRUS) biopsies of the prostate if the percent free PSA was less than 27%. The primary endpoint evaluated was prostate cancer detection in high-risk men with a benign prostate examination, a normal total PSA between 2 and 4 ng/mL, and percent free PSA less than 27%. They concluded that a percent free PSA of less than 27% was found to be useful for detecting early-stage prostate cancers in men with a total PSA value between 2 and 4 ng/mL and normal DRE findings.[21]

Prashant Shrivastava et al studied the role of urinary PSA and urinary micro-semino protein beta in Seventy-seven patients. They were divided into two groups: 32 had PCa (Group A) and 45 had no cancer (Group B) on biopsy. The median (interquartile range) serum PSA was 49.6 (0.2–254) ng/ml. The median urine PSA (29.5 vs. 26.4 mg/dl) and MSMB (1.7 vs. 2.4 mg/dl) were similar in both groups at baseline. However, post-DRE, both these metabolites rose in Group B but not in Group A, resulting in significantly higher post-to-pre values in Group B versus Group A. The post-DRE urine PSA/MSMB ratio was also significantly different between the groups.[22]

6.3 AIMS AND OBJECTIVES OF THE STUDY

- To determine the association of urinary PSA in differentiating benign prostate hyperplasia and carcinoma prostate.
- To study its role in diagnosis of carcinoma prostate in cases when serum PSA is in equivocal range.

7.0 MATERIALS AND METHODS

After clearance from institutional ethical committee and informed written consent from all those patients who fulfill the criteria will be taken up for the study.

7.1 SOURCE OF DATA:

This prospective study will be conducted in department of Urology & Kidney transplant both inpatient and outpatient at Dayanand Medical College & Hospital from March 2020 to February 2021.

7.2 METHOD OF COLLECTION OF DATA

Inclusion Criteria

- Patients of age group between 50-80 years presenting with lower urinary tract symptoms.
- Increased S.PSA level(4-10ng/ml)
- 24 hours of last ejaculation

Exclusion criteria

- Active urinary tract infection,
- Patients with features of prostatitis,
- Diagnosed case of carcinoma prostate,
- Prostatic abscess,
- Recent urinary tract instrumentation.

Demographic profile of all the patients will be noted down.

Parameters studied

All those patients who have S.PSA > 4 ng/ml (upto 10 ng/ml) or abnormal digital rectal examination will undergo TRUS guided prostate biopsy. A urine sample before digital rectal examination and immediately after will be collected for urinary PSA level. During DRE, whole of the prostate gland will be pressed sufficiently from all the sides. The urinary samples collected will be analyzed by the standard biochemical analyzers. Pre DRE and post DRE urinary samples will be labeled separately.

Patients diagnosed with carcinoma prostate will be labeled as group A and those who will be diagnosed as BPH as group B.

OUTCOME: There are no standard guidelines regarding the evaluation of patients with serum PSA in the range of 4-10 ng/ml associated with normal digital rectal examination. In this study, we will try to establish the role of urinary PSA in the diagnosis of carcinoma prostate, there by, limiting the need for prostate biopsy and other radiological investigations such as MP MRI/ PSMA PET CT scan in every case.

STATISTICAL ANALYSIS: Data were described in terms of range; mean ±standard deviation (± SD), median, frequencies (number of cases) and relative frequencies (percentages) as appropriate. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using SPSS (Statistical Package for the Social Science) SPSS 21 version statistical program for Microsoft Windows.

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

Yes,

Pre DRE investigations include: complete hemogram, coagulation profile, urine routine, urine culture, urine PSA

Post DRE investigations: urine PSA and transrectal USG for prostate biopsy

Histopathological examination of prostate biopsy.

7.4 HAS ETHICAL CLEARENCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

Applied for.

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PROFORMA

Sr No._____

Name_____ Age_____

MRD_____

C/O_____

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HOPI_____

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_____

_____

Pasthistory_____

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PersonalHistory_____

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Other significant history_____

Signature of Candidate **Signature of Supervisor**

General physical examination

P/A

DRE

Signature of Candidate **Signature of Supervisor**

INVESTIGATION

Hb TLC PLT

Sr Urea Sr Creatinine Coagulation profile (PTI/INR)

Urine Examination (routine and culture)

Ultrasonography- KUB and prostate……..

Serum prostatic specific antigen……..

Urine prostate specific antigen:

Pre DRE	Post DRE

Histopathology Report:

Signature of Candidate **Signature of Supervisor**

INFORMED PATIENT CONSENT

Date: _____

I.....D/o, W/o, S/o.....
.....am willing to participate in the study **"EVALUATING THE ROLE OF URINARY PSA IN DIFFERENTIATING BENIGN PROSTATE HYPERPLASIA FROM CARCINOMA PROSTATE"** The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason.

.....
Signature of the Witness

.....
Signature of the patient

Name:

Signature of Candidate

Signature of Supervisor

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____

निवासी _____

इस शोधकार्य **"EVALUATING THE ROLE OF URINARY PSA IN DIFFERENTIATING BENIGN PROSTATE HYPERPLASIA FROM CARCINOMA PROSTATE"** में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

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गवाह के हस्ताक्षर

नाम:

_____

रोगी के हस्ताक्षर/अंगूठे का निशान

नाम:

_____

अन्वेषक के हस्ताक्षर

_____

विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ_____

ਵਾਸੀ _____

"EVALUATING THE ROLE OF URINARY PSA IN DIFFERENTIATING BENIGN PROSTATE HYPERPLASIA FROM CARCINOMA PROSTATE" ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

_____ _____

ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____ ਮਿਤੀ_____

ਪਤਾ _____ ਪਤਾ _____

_____

ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

_____

ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ